THE MEDICAL JOURNAL OF AUSTRALIA

VOL. I.—37TH YEAR. SYDNEY, SATURDAY, JUNE 24, 1950. No. 25.

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THE CLINICAL SIGNIFICANCE OF SODIUM AND POTASSIUM ANALYSES OF BIOLOGICAL FLUIDS: THEIR ESTIMATION BY FLAME SPECTROPHOTOMETRY.

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IN clinical practice cases in which water and electrolyte balance is grossly abnormal are frequently encountered. The mortality in these cases is still high. This is largely because the biochemical information generally available to the clinician is insufficient for an accurate assessment of the disorder and for the adequate control of treatment. Whilst a knowledge of the disorder of physiology being treated and informed clinical judgement suffice in the treatment of many patients, and are essential in the treatment of all, severe cases of water and electrolyte disturbance require more than this. Adequate and relevant biochemical information is required. Sodium and potassium analyses of biological fluids provide an essential part of this information. The large mass of recent literature on this subject amply testifies to this fact.

Flame photometry is a method which enables sodium and potassium analyses to be performed rapidly and accurately. In the past the information provided by these analyses has not been speedily available because of the time required for the performance of the chemical methods. This has led to the widespread use of methods of "prediction" in an attempt to obtain equivalent information without directly estimating the sodium and potassium concentrations. Thus the chloride ion can be readily estimated and it is used to "predict" the more important sodium value. Similarly the acid-base balance of the blood is "predicted" from the plasma bicarbonate value alone. In many cases these "predictions" involve dangerous assumptions. The clinical "rules" and "hydration formulæ" which are used in an understandable attempt to simplify the problems associated with the management of cases of water and electrolyte imbalance are largely based upon these assumptions, and hence may be equally dangerous. The use of "hydration formulæ" in the place of adequate biochemical assessment has resulted in patients' receiving "routine" therapy rather than therapy designed to meet their individual needs. The high mortality rate in severe cases of water and electrolyte imbalance demands a more vigorous attack upon this problem than has been the case in the past. The present paper has been written from this point of view.

There are two sections to the paper. In the first section the clinical significance of sodium and potassium estimations is discussed. For reasons of space details of our own cases are not cited as examples, but will be published separately. The discussion has been written with three points in mind. First, we are concerned with cases of severe water and electrolyte imbalance. Second, it is necessary that the sodium and potassium analyses be quickly available—this involves the use of a flame photometer. Third, the biochemical facilities must be adequate to provide other relevant information such as pH, specific gravity, hæmatocrit, hæmoglobin total protein, chloride and bicarbonate values, *et cetera*, of the appropriate body fluids.

The second section of the paper describes sodium and potassium analyses of biological fluids by means of the Beckman flame spectrophotometer. Our results are given in detail, since at the present time no full account of such

[1] Assisted by funds provided by the National Health and Medical Research Council.

analyses with this instrument has appeared. When necessary, comparisons are drawn between the results we have obtained and the experiences of others who have been using different types of flame photometers.

SECTION I. THE CLINICAL SIGNIFICANCE OF SODIUM AND POTASSIUM ESTIMATIONS.

The situations in which the clinician requires biochemical information fall into two categories—emergency and non-emergency cases. In the former the time factor is an important consideration if the patient is to derive any benefit from the information. We will consider these two situations separately.

Medical and Surgical Emergencies.

Severe water and electrolyte imbalance endangering life may develop rapidly in a number of clinical conditions —for example, diabetic coma, acute renal failure, severe loss of alimentary secretions, acute adrenal cortical insufficiency, severe burns *et cetera*. In all these conditions restoration of the normal body fluid pattern is a major aim of the clinician. The management of these patients involves a rapid quantitative assessment of the biochemical disorder and measures to correct it. There may be two separate phases in the treatment of these patients. The first phase is correction of the existing biochemical disorder, and the second phase is the maintenance of a state of equilibrium if the stress continues—for example, uncontrolled ketosis, the loss of a large amount of alimentary secretion, or profuse diuresis *et cetera*. Treatment must be designed so that it does not itself constitute an unnecessary stress on the body's homœostatic mechanisms. This is because the functions of the organs upon which these mechanisms depend may be grossly impaired, even if only temporarily, by the initial pathological process or the physiological and biochemical disorders arising from it. Disregard of this principle accounts for many fatalities in these cases.

In attempting to restore a normal water-electrolyte pattern throughout the body, the clinician is concerned first with the extracellular fluid—the *milieu intérieur*—since it can be anticipated that changes in the extracellular fluid will be accompanied by the appropriate type of change in the intracellular fluid. However, there is this exception, that if there is gross depletion of intracellular electrolytes, such as potassium, this will need to be replaced before the intracellular fluid will become normal, and in fact before the changes in the extracellular fluid can be adequately corrected (Darrow, Schwartz, Iannucci and Colville, 1948; Darrow, 1948).

Analysis of the available portion of the extracellular fluid—the blood plasma—may provide much information upon which rational therapy can be based. The sodium ion plays a predominant role in the chemical anatomy and physiology of the extracellular fluid, since its concentration largely determines (*a*) the electrolyte osmotic pressure, (*b*) the total volume, and (*c*) the acid-base balance of this fluid. We shall consider briefly these three aspects of the extracellular fluid pattern and the reasons for assigning to the plasma sodium estimation considerable importance as a diagnostic aid in cases of gross water and electrolyte imbalance.

The Significance of Plasma[1] Sodium Estimations in Clinical Emergencies.

Plasma Sodium Content as an Index of Electrolyte Osmotic Pressure.—The electrolytes are the major osmotically active components of the body fluids (McCance, 1936; Peters, 1935; Gamble, 1947). The osmolar value of the electrolytes depends upon the sum of the ionic concentrations. However, the anion values are adjusted to the total cations by means of reciprocal alterations in anion concentrations, as is seen, for example, between the bicarbonate and chloride ions. Hence it is the cation values which primarily determine the electrolyte osmotic pressure of the body fluids. The total cation concentration may therefore be regarded as the primary dependent variable as far as the electrolyte osmotic pressure is concerned. Sodium is the major component of the cations of the extracellular fluid (approximately 94%), and potassium of the intracellular fluid. Consequently these two ions play a dominant role in determining the quantity of water in the two main fluid compartments. Acute stresses on ionic homœostasis involve in the first instance the extracellular electrolytes. Consequently it is the alteration in the level of the sodium ion which then largely determines the movement of water between the intracellular and extracellular fluid. This is true whether the alteration is produced by the disease or by the therapeutic measures being used. Since the plasma sodium concentration is an adequate criterion of the electrolyte osmotic pressure of the extracellular fluid, the clinician may be guided by this in deciding the appropriate electrolyte concentration of the replacement fluid. Consider, for example, the condition in which water is lost in excess of electrolytes. Gross degrees of this condition are frequently seen—for example, in some cases of diabetic coma. The extracellular fluid is hypertonic (raised plasma sodium content) with a moderate reduction in volume. The infusion of large volumes of isotonic saline may have disastrous consequences. The extracellular hypertonicity is little reduced by this treatment, and under these circumstances very little water can pass into the cells where it is required. The extracellular fluid volume therefore expands, increasing the cardiac burden. Moreover, the unnecessary electrolyte load places an additional strain on the renal mechanism, already committed by the primary water deficit to the excretion of a minimum volume of urine.

The converse condition of depletion of electrolytes in excess of water tends to cause hypotonicity of the extracellular fluid and considerable reduction in its volume. The infusion of a solution hypotonic with regard to its electrolyte concentration cannot restore the extracellular fluid volume, and in fact may cause it to fall further, as electrolytes are lost in the resulting diuresis. Death from peripheral circulatory failure may occur in these cases.

Therapeutic errors such as those just described are still encountered and could be avoided if the relevant biochemical information was available at the time when it was required. Plasma sodium estimations provide a valuable part of this information. Two points must be stressed. First, it is important to recognize that the chloride ion concentration cannot be used safely in the same way as the sodium concentration in order to depict the electrolyte osmotic pressure of the extracellular fluid, since it is not a primary dependent variable in the water-electrolyte relationship. This point will be elaborated further in a subsequent section. Second, the plasma sodium concentration alone is not an adequate criterion of the total amount of sodium in the extracellular fluid; but it can be used to determine this important value, and we will now consider this.

Plasma Sodium Content and Plasma Volume as an Index of the Total Amounts of Extracellular Water and Electrolytes.—In attempting to depict the total amounts of water and electrolytes in the extracellular fluid from plasma electrolyte concentrations, it is necessary to have some measure of the contraction or expansion of the extracellular fluid volume. This is so because when water and electrolyte balance is upset, several mechanisms, operating to maintain a normal electrolyte osmotic pressure (predominantly sodium concentration), may cause the volume of the extracellular fluid to vary over a wide range. When the state of hydration is changing rapidly, alterations in the extracellular fluid volume are generally reflected in corresponding changes in plasma volume, except in some cases of œdema and peripheral circulatory failure. In the absence of anæmia, the hæmatocrit value (the volume fraction of packed red cells in whole blood) may be used as an index of hæmoconcentration, from which alterations in plasma (and by inference the total extracellular fluid) volume may be deduced. Similarly changes in plasma protein concentration may be used as an index of alteration in plasma volume, except when the hæmoconcentration is due to the loss of a protein-rich fluid, as in burns, when

[1] In the following discussion the plasma sodium concentration is assumed to equal the sodium concentration of the interstitial fluid, the difference due to the Donnan equilibrium being ignored. We have also followed the practice of expressing electrolyte concentrations in terms of whole plasma rather than in terms of plasma water.

the plasma protein concentration falls despite hæmoconcentration.

In practice we have found the hæmatocrit and plasma protein values a useful guide to alterations in plasma volume in most cases, particularly when serial observations are made during the course of treatment. This information can be correlated with the plasma sodium concentration in order to depict the total amounts of water and electrolytes in the extracellular fluid. Restoration to normal of the hæmatocrit, plasma protein content and plasma sodium content indicates that the extracellular fluid volume and sodium content are largely normal. However, difficulties in applying this general formulation are encountered if there is a preexisting severe abnormality in red cell mass, in plasma protein concentration or in both. However, additional information obtained from the clinical condition of the patient, and particularly from urine analysis, usually enables the plasma estimations to be interpreted with confidence. The significance of urine analysis will be discussed subsequently.

Plasma Sodium in the Evaluation of Acid-Base Balance.—The sodium ion constitutes approximately 94% of the total base of the extracellular fluid, and therefore forms the main buffer base of this fluid. In treating a condition of abnormal acid-base balance, it is therefore essential to restore to normal the concentration and total amount of sodium in the extracellular fluid. Hence a correct evaluation of the acid-base balance depends, amongst other things, upon a knowledge of the level of the extracellular (plasma) sodium. We will discuss this subject further in a later section.

Thus the plasma sodium concentration provides much information upon which accurate replacement therapy can be based in conditions in which there is distortion of the water-electrolyte pattern. It is worth while to consider some common clinical procedures which are frequently used in an attempt to obtain equivalent information without estimating the sodium concentration itself.

The "Indirect" Estimation of Plasma Sodium Content.

The Prediction of Plasma Sodium Content from Plasma Chloride Content.—It is a common clinical practice to express the result of an analysis for the chloride ion as milligrammes of sodium chloride and to use this as a guide to the sodium concentration. This implies a fixed ratio of sodium to chloride in the body fluids and carries further the implication that the body treats sodium and chloride as "salt". Hence the use of the term, "salt" depletion. Cushny (1917) criticized the practice of expressing chloride titrations as sodium chloride. Gamble (1947) emphasized that the word "salt" has no biological meaning, and demonstrated that sodium and chloride ions might be treated separately by the body's homœostatic mechanisms. The sodium concentration of the extracellular fluid is maintained more nearly constant than the concentration of the individual anions because there is not the same possibility of large reciprocal changes of concentration in the cations as there are, for example, between the chloride and bicarbonate anions. In conditions of severe water and electrolyte imbalance the extracellular chloride concentration may be raised, normal or low, the sodium concentration varying unpredictably in the opposite direction (McCance, 1936; Marriott, 1947; Hoffman and Osgood, 1941-1942). Hence the chloride concentration is not a reliable criterion of the sodium concentration, and cannot be used safely to give equivalent information to the sodium concentration in conditions of water and electrolyte imbalance. The failure to recognize this principle has done a great deal to discredit the value of plasma estimations in the management of these patients.

The Prediction of Plasma Sodium Content from Chloride plus Bicarbonate.—Hald, Heinsen and Peters (1947) have investigated the problem of predicting plasma sodium content from chloride *plus* bicarbonate content. Normally the sum of plasma chloride and bicarbonate expressed as milliequivalents approximately equals the plasma sodium concentration *minus* 12 to 15 milliequivalents. The chemical methods for the estimation of the former two ions are not difficult or time-consuming, as is the case with chemical sodium estimations. Hence clinicians frequently rely upon the estimation of chloride and bicarbonate as a guide to the sodium level in pathological conditions. However, in the cases investigated by Hald, Heinsen and Peters (1947), the predicted sodium concentration under-estimated the actual sodium value by more than 10 milliequivalents per 100 millilitres (23 milligrammes of sodium per 100 millilitres) in 28% of their cases, which were not chosen for the severity of the water-electrolyte imbalance. If the biochemical findings in reported cases of severe water-electrolyte disturbance are examined, many examples will be found in which the error in the predicted sodium content is much greater—up to 30 milliequivalents per 100 millilitres (69 milligrammes per 100 millilitres). This is because there may be a large increase in the "undetermined anion" fraction, mainly by an increase of organic acids and phosphate, and a considerable alteration in the base equivalent of plasma protein, so that the combined chloride and bicarbonate concentrations represent a smaller fraction of the total anion equivalents than is usually the case. For this reason plasma analyses of chloride and bicarbonate can give misleading information when used to predict the level of plasma sodium.

The Prediction of Acid-Base Balance from Plasma Bicarbonate Content.—Since the base-equivalent of the plasma bicarbonate is available for combining with metabolic acids, the bicarbonate concentration is called the "alkali reserve" (Van Slyke and Cullen, 1917). A low "alkali reserve" alone is commonly regarded as indicating "acidosis" and a high "alkali reserve" as indicating "alkalosis", although this was never implied by Van Slyke and Cullen. The plasma bicarbonate content is only one variable of several dependent variables which must be defined for an accurate depiction of the acid-base balance of the blood. Reduction of the "alkali reserve" is not proportional to depletion of fixed base unless the acidosis is due solely to the loss of fixed base—for example, acidosis following the loss of a large amount of an alkaline secretion such as pancreatic juice. A low plasma bicarbonate level may be due to a retention of other anions (chloride, organic acids, phosphate, sulphate), the fixed base of the body fluids being normal or even raised. In some cases it is a compensatory adjustment to the excessive lowering of the partial pressure of carbon dioxide in the arterial blood owing to hyperventilation. But not infrequently it is found that a low "alkali reserve" has been taken as indicating a severe depletion of total fixed base, and that the patient has been given large amounts of sodium-containing fluids in consequence, with the attendant hazards of hyperhydration, cardiac embarrassment, and even death. The over-estimation of the base deficit in such conditions as diabetic coma has been stressed often (Kety, Polis, Nadler and Schmidt, 1948; Singer and Hastings, 1948; Abbott, 1946; Lockwood and Randall, 1949), and is largely to be attributed to a failure to recognize the limited nature of the information provided by a serum bicarbonate estimation in the absence of knowledge of other variables, such as the level of total base (predominantly sodium). In the converse situation of "alkalosis", as may occur with the loss of a large volume of gastric juice, a normal "alkali reserve" may be present with a considerable depletion of sodium, and may therefore give entirely misleading information on the acid-base balance in the extracellular fluid. Plasma sodium estimations can provide the information necessary to avoid over-estimation of base deficit in "acidosis" and its under-estimation in "alkalosis".

The Significance of Urinary Sodium Estimations in Clinical Emergencies.

The plasma concentration of the electrolytes represents the final result of a number of mechanisms operating to maintain homœostasis in the *milieu intérieur*. As the kidney plays a predominant role in maintaining the equilibrium state of the water-electrolyte pattern of the body, the urine elaborated by a normal kidney gives quantitative information upon the state of the body fluids. Urine analysis is stated to be superior in this regard to plasma analysis (Marriott, 1947; Peters, 1947; Van Slyke and Evans, 1948). Such urinary estimations as the volume, specific gravity, pH and sodium and chloride concentrations

may give a clear picture of the biochemical stresses on the body and of the response to treatment, provided that renal function is normal. Since, as has already been pointed out, the sodium ion largely determines the distribution of body water and the acid-base balance of the extracellular fluid, in urinary analysis it is the sodium value from which in general the clinician derives most insight in conditions of water and electrolyte imbalance. It is a common clinical practice to infer the sodium concentration from the urinary chloride value, and we shall now critically examine this practice.

The Prediction of Urinary Sodium Content from Urinary Chloride Content.—The ease with which urinary chloride estimations of reasonable accuracy can be made (Fantus, 1936), and the absence of an equally simple quantitative test for sodium, led Marriott (1947) to formulate the following clinical rule in the management of patients suffering from water and electrolyte depletion. The excretion of a normal volume of urine containing 60 to 100 milliequivalents of chloride ion per litre (three to five grammes of sodium chloride) indicates the adequate replacement of water and "salt" in an adult who is not suffering from adrenal cortical insufficiency.

While this rule has in general been very useful in clinical practice, nevertheless the criticism can be made that in some cases it is not consistent with the physiology of the condition being treated.

Firstly, it implies that the patient's requirements for sodium and chloride are quantitatively related, so that the excretion of a normal amount of chloride in the urine indicates the absence of "salt" (that is, sodium and chloride) depletion in the extracellular fluid. But sodium and chloride are frequently lost from the body in quantities which are not proportional to their concentrations in the extracellular fluid. Subtraction acidosis or alkalosis results, depending upon whether the loss favours cation or anion deficit. Elsewhere (Denton, 1949; Denton, Wynn, McDonald and Simon, in preparation) it has been shown that when sodium is subtracted from the body in excess of chloride, relative to the normal extracellular ratio of these two ions, the ratio of chloride to sodium in the extracellular fluid remains constant. This is because the kidney excretes chloride in excess of sodium commensurately with the stress. This mechanism controlling the extracellular electrolyte pattern operates independently of whether there is total depletion of sodium and chloride ions, and independently of whether their plasma levels are reduced below the so-called "renal threshold". In severe cases of this type there may be a hundred times more chloride than sodium in the urine even though there is no intake of these ions. When sodium and chloride are infused in equivalent quantities (saline), the chloride excretion may rise further. It is clear therefore that in these cases the urinary chloride titration has not the significance attributed to it in Marriott's rule. However, rising concentrations of sodium in the urine indicate the correction of sodium depletion in the extracellular fluid. In the converse situation, when chloride is subtracted from the extracellular fluid in excess of sodium, the urinary chloride excretion may be reliable as far as total depletion of chloride is concerned, but gives no information on the level of sodium. The infusion of saline until normal amounts of chloride appear in the urine may result in a dangerously excessive administration of the sodium ion. Urinary and plasma sodium estimations are of value as a guide to safe rates of administration of saline in these cases.

The second assumption is that there is a fixed "renal threshold" for chloride, so that chloride is excreted in the urine if its concentration in the plasma is above the "threshold", and that it is not excreted if its concentration is below the "threshold". Apart from the situation of excess sodium subtraction already cited, there are other cases in which the concept of a "renal threshold" for chloride does not apply.

In addition (metabolic) acidosis—for example, diabetic coma—there may be marked retention of chloride. Chloride may be absent from the urine despite raised plasma chloride concentrations and a normal urine volume (McCance and Lawrence, 1935; Atchley and Benedict, 1930; Peters, Kydd, Eisenman and Hald, 1933; Denton, Wynn, McDonald and Simon, in preparation). The reason for this chloride retention is not known.

The converse situation, in which large amounts of chloride are excreted in the urine despite severe hypochloræmia, has been described by Maddock (1939), by Power, Petersen and Maddock (1942), and by Ariel, Abels, Pack and Rhoads (1943). In these cases prolonged water and electrolyte depletion has usually been associated with some other feature, such as hypoproteinæmia, nitrogen depletion, prolonged sepsis, chronic hæmorrhage and renal or hepatic damage. Potassium depletion may have been an important factor (Darrow, Schwartz, Iannucci and Colville, 1948). Urinary chloride estimations in such cases would give very misleading information on the state of the body fluids. There is insufficient evidence in the reported cases to indicate whether the urinary sodium analyses would be equally misleading.

It is clear, then, that in many cases of water and electrolyte imbalance the patient's need for sodium may be quantitatively quite different from his need for chloride ion, and that the results of a test for chloride in the urine may not reflect the conditions of sodium balance. Greater certainty in the therapeutic measures can be based on the interpretation of the results of urinary analysis when this includes the estimation of urinary sodium excretion.

Conditions in which Renal Regulation of Electrolytes is Abnormal, and Plasma Analyses are Necessary.

There remains to consider two further groups of cases. In the first group urine analysis, whether of sodium or of chloride, may give misleading information on the water and electrolyte balance of the body. Coller, Campbell, Vaughan, Iob and Moyer (1944), and Wilkinson, Billing, Nagy and Stewart (1949), have demonstrated retention of sodium and chloride in some cases in the immediate post-operative period. Coller, Campbell, Vaughan, Iob and Moyer called the condition "post-operative salt intolerance" and stressed the possible dangers of over-administration of saline if reliance was placed upon urinary analysis as an index of adequate replacement of electrolytes. The converse situation is seen in adrenal cortical insufficiency, in which high urinary sodium and chloride concentrations may occur in the presence of considerable depletion of these ions in the extracellular fluid.

In the second group, analysis of urine is not practicable because of anuria or severe oliguria. Renal function is frequently abnormal in cases of severe imbalance of water and electrolytes, and may be very slow in responding to treatment (McCance, 1936; Marriott, 1947). In some cases it may amount to complete anuria, described by McCance (1936) as "mysterious anuria". Further, water and electrolyte imbalance may be associated with an organic renal lesion, leading to prolonged anuria or oliguria. Specific mention may be made of the syndrome of "lower nephron nephrosis" which may follow many types of trauma. (Burch and Ray (1949) have recently reviewed the extensive literature on this subject.) In many of these cases recovery can be expected provided the patient can be kept alive for a period long enough for the tubular damage to be repaired, and for renal function to be reestablished. Accuracy in determining the water and electrolyte requirements is essential. The cause of the death of many patients who die during the first fourteen days is acute pulmonary œdema due to over-administration of sodium-containing fluids (Fields *et alii*, 1949; Bull *et alii*, 1949).

In these two groups of cases it is from plasma, and not analysis of urine, that most information upon the water and electrolyte requirements of the patient can be gained.

Sodium Estimations of other Biological Fluids.

Having corrected an initial biochemical disorder, the clinician may be confronted with a continuing stress—for example, the loss of large volumes of alimentary secretions.

In this case the loss may amount to several litres of fluid per day, rapidly leading to severe depletion of water and electrolytes. However, if the fluid being lost can be collected, its volume measured and its ionic composition determined, a quantitative estimate of water and electrolyte requirements is available upon which accurate replacement therapy can be based. The advantage of sodium estimations of such fluid is obvious.

Non-Emergency Situations.

The Role of Sodium Estimations.

In the group of cases in which no emergency exists, speed in the actual determination is not a vital factor. However, since the standard chemical determinations are time-consuming, it is not usually practical to request the routine hospital laboratory to undertake any large number of sodium or potassium estimations. Hence these estimations are frequently not made, and in some cases the success of the therapeutic procedure is prejudiced. A good illustration of this is seen in the use of dietary sodium restriction in the treatment of cardiac and renal œdema, hypertension, toxæmia of pregnancy *et cetera*. It is difficult in out-patient practice for the patient to be certain that his dietary intake of sodium remains within the limits prescribed by his physician. Since diets low in salt content are unpalatable to the majority, and adherence to the diet usually entails considerable sacrifice by the patient, it is a necessary part of the treatment that the urinary output of sodium should be estimated at frequent intervals so that the efficacy or otherwise of the dietary régime can be determined. The use of the urinary chloride estimation as a guide to sodium excretion in these cases has been recommended (Bryant, Iob, Phillips and Blecha, 1949). However, analysis of their figures shows that the errors involved in assuming that the sodium and chloride excretions are commensurately related are not inconsiderable in many cases, and moreover the chloride estimation would be of no value in cases in which salt substitutes containing chloride were being used. With the flame spectrophotometer, urinary sodium estimations can be accurately and rapidly made. The results of the determinations can be available within a short time of the patient's presenting for examination. From the results the physician can be guided as to the effectiveness of the dietary régime and the patient advised accordingly.

Similarly, measures undertaken to produce diuresis in cases of œdema should be judged according to the amount of sodium eliminated rather than by the volume of urine passed. If this were done as a routine measure, diuretics which fail to cause a reasonable excretion of sodium would be given up.

In the diagnosis of adrenal cortical insufficiency various tests are suggested, based upon the study of the chloride excretion under prescribed conditions. Since it is not at all clear that the chloride ion is controlled in the same way as the sodium ion by the adrenal cortical hormone (Leaf and Couter, 1949) it is not surprising that such tests are of decidedly limited usefulness, particularly in the diagnosis of early cases. A balance study involving an estimate of the oral intake and urinary excretion of sodium over a period provides accurate information for the diagnosis of adrenal cortical insufficiency. Conditions simulating adrenal cortical insufficiency, such as "salt-losing" nephritis (Thorn, Koepf and Clinton, 1944), acute porphyria (Prunty, 1949), tuberculosis and some myasthenic conditions (Broch, 1945), in which the adrenal gland is not involved, can be distinguished from Addison's disease by a study of the sodium balance and the effect upon it of adrenal cortical hormones.

The Role of Potassium Estimations.

During the last decade considerable emphasis has been placed upon the part played by the potassium ion in disease. The main loss of potassium from the body occurs in the urine. The kidney does not reabsorb all the potassium in the glomerular filtrate. Hence potassium loss is continuous, and when intake is deficient, or there is profuse diuresis, potassium depletion occurs. This is greatly increased in chemical stresses which cause release of potassium from cells—for example, disproportionate electrolyte subtraction, metabolic acidosis, starvation, water deprivation, and Cushing's syndrome. Considerable amounts of potassium may be lost in alimentary secretions, particularly gastric juice, and depletion may also be caused by prolonged extrarenal dialysis with non-potassium-containing fluids (Wener and de Leeuw, 1949). Darrow (1945) has clearly demonstrated the importance of adequate potassium replacement therapy in the management of patients with potassium depletion.

Hypokalæmia (low extracellular potassium concentration) may be associated with potassium depletion, although it is not a necessary feature of such a condition (Denton, Wynn, McDonald and Simon, in preparation). It may occur also without total body depletion, as in familial periodic paralysis (Aitken, Allot, Casteden and Walker, 1937-1938). The dramatic effects of hypokalæmia in producing muscle weakness and respiratory paralysis in diabetic coma were first described by Holler (1946). Since then numerous reports attributing death in diabetic coma to untreated hypokalæmia have appeared.

The converse situation of potassium intoxication with high plasma potassium values (hyperkalæmia) may occur in cases of prolonged anuria, in chronic renal failure, and

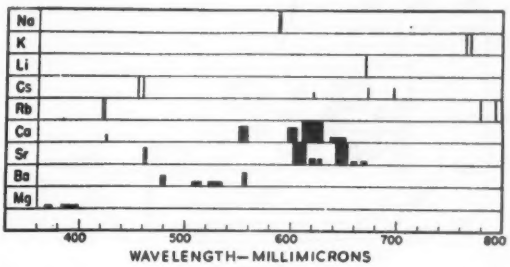

FIGURE I.

Characteristic flame spectra produced in illuminating gas flame.

in cases in which potassium therapy is being employed. Patients with cardio-renal failure receiving potassium salts as diuretics come into this third category (Stewart, Shepard and Morger, 1948). Hyperkalæmia may cause serious disturbance of cardiac function and even death, and must be guarded against in the treatment of renal failure and when potassium salts are used in therapy.

In clinical work, the main value of plasma potassium estimations is in the diagnosis of hypokalæmia and hyperkalæmia, and in the control of the rate of potassium administration in cases of potassium depletion. A striking example of the value of plasma potassium estimations is seen in the treatment of diabetic coma. When the patient is examined early in coma, the plasma potassium level is usually normal or slightly raised, and potassium is being released from the cells. During the course of treatment the extracellular potassium level falls for the following reasons. Correction of the acidosis and water depletion cause potassium uptake by the cells. Some potassium is bound in the liver and muscles, associated with the reformation of glycogen and protein due to insulin activity. Large infusions of potassium-free fluids dilute the extracellular fluid, thus accentuating hypokalæmia. By following these dynamic changes in the distribution of potassium, as revealed by plasma analyses, the clinician has a guide to the appropriate time and rate of administration of potassium in the treatment of these patients.

Potassium estimations in urine, and in gastro-intestinal secretions such as gastric juice, are of value in some cases in giving an accurate estimation of potassium losses, which must be replaced if potassium depletion is to be avoided. A persistently high level of urinary potassium excretion in a patient who has had no food or other source of potassium intake for some days may be taken as indicating the probability of potassium depletion and the need for adequate replacement therapy. When potassium is

administered parenterally, the urinary potassium estimation is useful to indicate whether a positive balance of potassium has been achieved.

In this first section the clinical importance of sodium and potassium analyses of biological fluids has been discussed. In the second section a method—flame spectrophotometry—which enables these analyses to be rapidly and accurately performed will be described.

SECTION II. PRINCIPLES OF FLAME PHOTOMETRY.

The property which certain elements have of emitting characteristic radiation when excited by high temperatures or by electrical means forms the basis of emission spectroscopy. In the past, various methods have been employed to produce this radiation—for example, spark, arc, flame, and discharge tubes (Brode, 1943). Each method has certain advantages for different elements, and the emission spectrum is in part dependent upon the excitation method employed. For the clinically important elements, sodium,

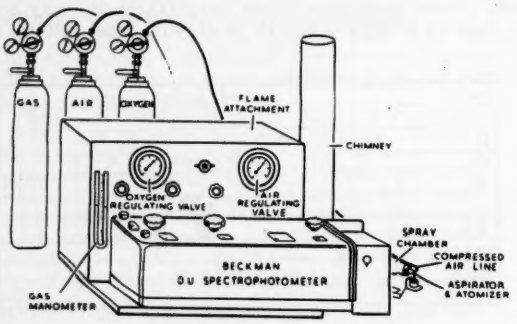

FIGURE II.

The assembled Beckman flame spectrophotometer viewed from the front (semi-diagrammatic).

potassium and calcium, the flame method has the advantages of simplicity and ease of sample preparation. In the flame, sodium and potassium emit atomic line spectra of characteristic wave-length. The calcium spectrum is more complex and is largely due to the molecular band spectrum of calcium oxide.

Figure I shows the emission spectra in the air-illuminating gas flame of some of the alkali and alkaline earth metals. When an atomized vapour of an aqueous solution of one of these elements is introduced into the flame, the intensity of the spectral emission of the element is a function of its concentration, provided that steady flame conditions prevail, that the vapour is delivered into the flame at a constant rate, and that other substances are not present in the solution which directly enhance or depress the spectral emission of the element under test. The concentration of the element in the test solution can be determined by comparing its spectral emission energy with that of a solution of known concentration.

A flame photometer is an instrument consisting of the following parts: (i) an aspirator and atomizer, to deliver the test solution as an atomized vapour and at a constant rate into the burner; (ii) a burner assembly, in which a flame of constant thermal output can be maintained over a prolonged period; (iii) a monochromator, to isolate radiation of a selected wave-length characteristic of the element being determined; (iv) a photometric device to measure the energy of the incident radiation.

Different types of flame photometers have been described, the differences being mainly in the flame source (air-acetylene, air-gas,[1] oxygen-gas[1]), in the monochromatic system (colour filters, quartz prism), in the photometric device (photographic plate, photoelectric cell, phototube), and in the use of internal standards. Each type of instrument has certain characteristics, advantages and disadvantages.

[1] The common gases used are coal gas, illuminating gas, natural gas and propane.

The Beckman Flame Spectrophotometer.

The Beckman flame spectrophotometer is illustrated in Figures II and III.

1. The aspirator and atomizer are shown in Figure IV. The test solution in a small beaker is aspirated through a fine glass capillary, the distal end of which projects through a rubber stopper into a heated glass spray chamber. The aspirator is activated by a stream of compressed air at finely controlled pressure. A fine mist is formed which passes through the spray chamber into the base of the burner, and is then carried into the flame, where the material is ignited. The spray chamber is heated to prevent condensation of the vapour on the walls of the chamber.

2. The burner is a modified Méker type burner, and a mixture of oxygen and coal gas or natural gas provides the flame. We use bottled coal gas with a Heidbrink type

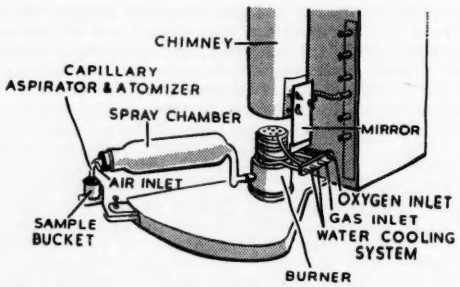

FIGURE III.

Rear view of the photometer to show the spray chamber and burner assembly. The electrical heating jacket which surrounds the spray chamber is not shown.

reducing valve and flow meter. The optimum pressures of oxygen and coal gas for each element must be determined. Once set, neither the gas pressure nor the oxygen pressure should vary throughout the period of the analysis.

3. The monochromatic and photometric system will now be described. Accuracy and freedom from certain types of interference in analyses by means of flame photometry largely depend upon the precision with which the optical system can resolve the incident radiation and isolate a narrow band at the desired wave-length. In the "Beckman Quartz Spectrophotometer, Model D.U.", the optical system is of high resolving power and selectivity. The band width resolution in millimicrons (mμ) is given by the formula $W_E = X.W_D + 0{\cdot}02\ W_D$ (manufacturer's bulletin 91-c), where:

W_E = Spectral band width to be used for measurement.
W_D = Spectral band width per 1·0 millimetre slit opening (from dispersion data supplied with the manufacturer's bulletin).
X = The actual slit width used at the wave-length selected.

For the sodium line at wave-length 589 mμ and a slit width of 0·1 millimetre, the band width selected is 4·0 mμ, and for potassium at wave-length 767 mμ and a slit width of 0·15 millimetre, it is 11 mμ. This ensures adequate isolation of the potassium and sodium line spectra.

The photometric system is provided by two phototubes, one with maximum sensitivity above 625 mμ, and the other below this wave-length. With the instrument set at the correct photometric sensitivity, the galvanometer needle moves about three scale divisions from the null point for a 1% alteration on the transmission scale. With proper adjustment, readings can be taken which should show a mean deviation from the mean not exceeding 0·5% of the reading at one-third or more of full scale.

Calibration Curves.

Without Interference.—For a single element ignited in the flame, the energy of emission is proportional to the concentration of the element in the test sample. Factors which may alter this simple relationship are called interference factors and will be separately considered. Before the unknown solution can be analysed, a calibration curve must be obtained. A set of standard solutions of suitable concentrations of the element under test is prepared in

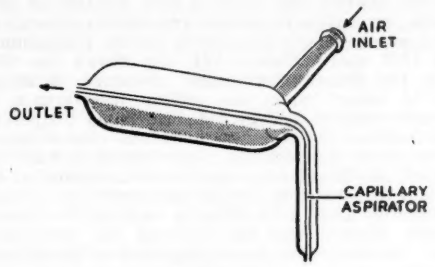

FIGURE IV.

The capillary aspirator and atomizer. Compressed air enters at the inlet. The high velocity of the air at the outlet causes a reduced pressure in the capillary (Venturi effect). The solution is aspirated up the capillary, converted into a fine mist by the air turbulence at the outlet, and carried by the stream of air into the burner.

distilled water. For example, sodium standards contain 1·0 milligramme, 0·8 milligramme, 0·6 milligramme, 0·4 milligramme, and 0·2 milligramme *per centum*[1] of sodium (analytical reagent sodium chloride being used).

The solution containing 1·0 milligramme *per centum* is fed into the flame, and the photometric sensitivity of the spectrophotometer is adjusted so that at the selected wavelength, slit width and gas, oxygen and air pressure, the incident radiation reads 100% on the transmission scale of the spectrophotometer. The remaining standard solutions

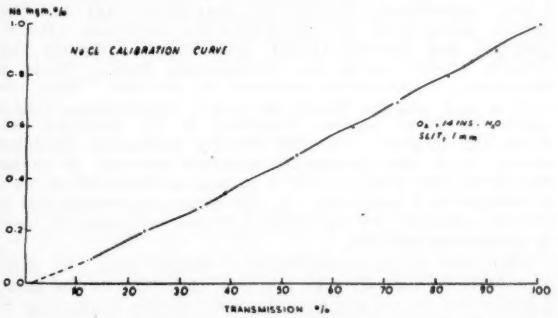

FIGURE V.

are then fed separately into the flame and the transmission energy of each is determined relative to the 1·0 milligramme *per centum* standard. In this way a sodium calibration curve can be constructed. The graph in Figure V shows the sodium calibration curve for concentrations between 1·0 and 0·0 milligramme *per centum*. There is practically a linear relationship over this range of concentration. The curve does not pass quite through the origin at zero concentration, because the flame background reads about 2% or less on the transmission scale. The contribution of the flame background to the transmission energy does not alter significantly during the course of the analyses. When it reads 2% or less, and the transmission energy of the test element reads above 75%, the error introduced by disregarding the background contribution is negligible. However, correction can be made by subtracting the flame background reading from the transmission readings of the standard and unknown solutions.

The graph in Figure VI is the calibration curve for sodium concentrations from 5·0 to 0·0 milligrammes *per centum* of sodium. The graph is now curvilinear.

The potassium calibration curve is linear for concentrations of potassium up to 2·0 milligrammes *per centum*. The lithium calibration curve is similar to this.

Standards are made up in bulk and kept in "Pyrex" flasks with ground-in glass stoppers. They can be kept in this way for several weeks without deterioration. The standard curves for each element do not vary provided the analytical conditions are kept constant, and theoretically it is quite reasonable, once a curve has been drawn up, to use only one standard, preferably the 100% standard, for subsequent analyses. In practice we always make a

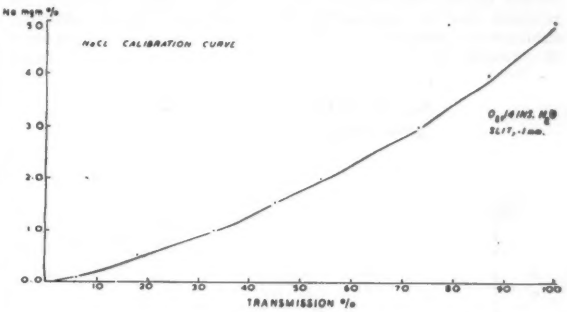

FIGURE VI.

complete calibration run each time the instrument is used. In this way a constant check on the instrument, standards and glassware can be obtained, since any error in the analytical procedure is readily revealed by the calibration curve's differing from the normal. Once a calibration curve has been obtained with known solutions, the test solution, diluted so that the concentration of the test substance falls within the range of the standards, and preferably as close as possible to the concentration of the 100% standard, is fed into the flame and its spectral emission energy is determined. The concentration of the element in the unknown can then be determined by reference to the standard curve. With simple solutions of sodium and potassium salts, accuracy to ± 1% is readily obtained if the usual precautions of volumetric semi-micro analysis are observed. The maximum accuracy is obtained when the concentration of the unknown reads above 75% on the transmission scale.

With Interference.—Four factors may interfere with the direct relationship between the emission energy of the element in the standard solution and the emission energy of the corresponding element in the test sample. These are: (i) differences in flame temperature during the course of the analysis; (ii) differences in rate of delivery of the standard and test samples into the burner; (iii) superimposition of emission energy of foreign substances in the unknown mixture upon the emitted radiation of the test substance; (iv) direct depression or elevation of the emission energy of the test substance by foreign substances in the unknown mixture.

1. The first factor is negligible in the Beckman instrument, because the rates of supply of gas, oxygen and air to the flame are closely controlled. Small temperature fluctuations have a negligible effect upon the spectral emission of the element in the flame.

[1] In referring to standard solutions which are made up with water the notation "milligrammes *per centum*" is used. The notation "milligrammes per 100 millilitres" is used to describe electrolyte concentrations in biological fluids. Following the usual clinical procedure, we have made no correction for varying amounts of protein in these fluids. The difference in notation serves to emphasize this point.

2. Differences in viscosity between the standard and test solutions are of considerable importance, since viscosity is a factor determining the rate at which the aspirated solution is delivered into the flame. The temperature of the oxygen-gas flame is such that the photometric sensitivity of the instrument is satisfactory at low concentrations of sodium and potassium, therefore the viscosity factor can be overcome by using high dilutions of the biological fluids. Calcium, however, because of its lower emission energy, cannot be estimated satisfactorily at high dilutions, and consequently viscosity limits the usefulness of this flame photometer in the estimation of calcium in plasma. The problem of viscosity will be referred to again in the discussion of sample preparation.

3. Since the monochromator of the Beckman instrument possesses such high resolution and selectivity, the third interference factor listed is of negligible importance in clinical work. The optimum wave-lengths of sodium at 589 mμ and of potassium at 767 mμ are so far apart that the monochromator has no difficulty in separating them. The calcium band near the sodium line causes no significant interference in sodium estimations, because sodium is estimated at dilutions and at a temperature at which spectral emission from calcium is negligible. However, sodium can interfere in calcium estimations. The highest proportion of calcium to sodium we have found in biological fluids occurred in the urine of a patient with gross acidosis due to post-gastrectomy duodenal fistula (sodium subtraction acidosis). In this case the ratio of sodium to calcium in the urine (in milligrammes *per centum*)

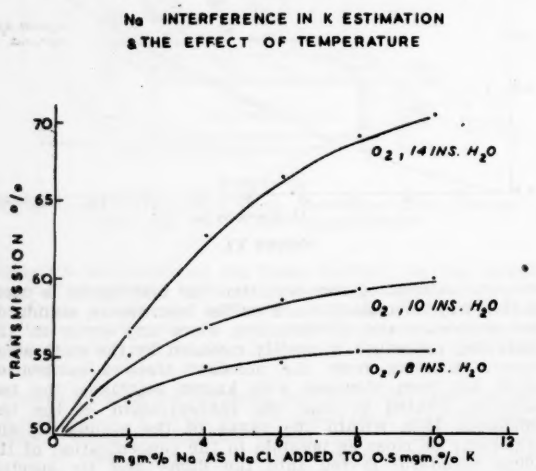

FIGURE VII.

was 1:20 (millimolar ratio 1:12). A solution of 1·0 milligramme *per centum* of sodium gives the same energy transmission as a similar solution containing in addition 20 milligrammes *per centum* of calcium in the form of calcium chloride. Consequently calcium does not interfere with sodium estimations in clinical work. This finding is at variance with the results of Domingo and Klyne (1949). They used a higher temperature air-acetylene flame and colour filters to isolate the sodium D line. They found the emitted energy to be the sum of the sodium and calcium spectra. They suggest that this interference effect is due to the inability of the filters used to separate the sodium line at 589 mμ from the calcium lines at 618 and 620 mμ. The high operating temperature is probably also a factor.

4. The emission energy of an element may be depressed or enhanced by the presence of other substances in the test solutions. In biological material in which sodium and potassium are being estimated, the substances whose possible interference would need to be considered are sodium in potassium estimations and *vice versa*, phosphates, calcium, ammonia, organic acids, urea, glucose, protein and lipides.

Sodium Interference in Potassium Estimations.—The graph in Figure VII shows the effect of adding increasing amounts of sodium (as chloride) to a constant amount of potassium upon the intensity of the potassium spectral line. The instrument is set so that a pure solution of 0·5 milligramme *per centum* of potassium (as potassium chloride) reads 50% on the transmission scale. The increased luminosity of the potassium ions produced by the addition of sodium is well shown and corresponds with the finding of Domingo and Klyne (1949), who used the air-acetylene flame. The increased spectral emission is not due to the sodium line, since a pure solution of 20 milligrammes *per centum* of sodium (as sodium chloride) gives a zero reading on the photometer at the potassium wavelength (767 mμ). Figure VII also shows the effect of varying the flame temperature (pressure of oxygen in inches of water) upon the sodium interference in the potassium emission energy. As the flame temperature is raised, sodium interference increases considerably. At the lower flame temperature (eight inches of water oxygen pressure), the interference reaches a maximum at a ratio of sodium to potassium (in milligrammes *per centum*) of approximately 16 to 1 (millimolar ratio 28:1). Increasing the ratio further does not increase the level of interference. At the higher flame temperatures the interference

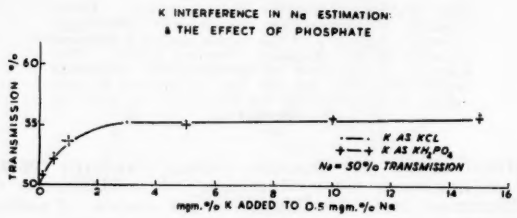

FIGURE VIII.

does not reach a maximum until the sodium–potassium ratio is considerably greater. The interference curve with the high-temperature air-acetylene flame (Domingo and Klyne, 1949) does not reach a maximum even at a millimolar ratio of 200 to 1. The influence of flame temperature is interesting and may explain why Hald (1947), using a low temperature (air-pyrofax gas) flame, did not find sodium potentiation of the potassium spectrum. Berry, Chappell and Barnes (1946), and Parks, Johnston and Lykken (1948), using low temperature flames, found a depression of potassium emission by sodium. With the oxygen and coal-gas flame, the lower temperature (eight inches of water oxygen pressure) is the optimum for potassium analysis. At this setting potassium emission energy in a pure potassium chloride solution is at its maximum, and when sodium is present sodium interference is reduced to a minimum. In the subsequent discussion it will be assumed that the lower pressure of oxygen is used in potassium analysis.

When the interference curve is plotted with the ratio of sodium to potassium as abscissa, the curve is the same whether 0·5 or 1·0 milligramme *per centum* potassium is used with increasing amounts of sodium. This demonstrates that at these two levels of potassium concentration the interference effect depends upon the ratio of the ions, and not upon their absolute amounts.

There are three important features of the interference curve which suggest three methods for overcoming the interference. The first feature is that the shape of the curve does not vary provided the experimental conditions remain the same. The second feature is that the interference reaches a maximum at a reasonably small sodium–potassium ratio. The third is that the interference depends upon the ratio of the ionic concentration.

Methods of Correcting Sodium Interference in Potassium Estimations.—The first method of correcting sodium interference in potassium estimations is to use the known interference curve, such as that shown in Figure VII. Sodium and potassium are estimated in the same sample by

means of pure sodium and potassium standards. From the found sodium to potassium ratio in the test sample and the interference curve, a correction factor can be derived and applied to the found value. Thus, suppose the found sodium to potassium ratio is 8:1. From the curve it can be seen that with this ratio the transmission energy of 0·5 milligramme *per centum* of potassium is increased from 50 to 52·5—that is, an increase of 5% of the theoretical value. It can be assumed that the transmission energy of the potassium in the unknown sample has been increased proportionately by the presence of the sodium. Let A equal the theoretical transmission value of the potassium in the test sample, B the found transmission value, and X the percentage increase in A as derived from the interference curve. Then $\frac{A + XA}{100} = B$. Therefore $A = \frac{100B}{100 + X}$. Hence the interference of the sodium in the test sample can be corrected and the actual potassium concentration in the test sample obtained. We shall give examples of the use of these interference curves when describing sodium and potassium estimations in urine. Two further points must be made. Firstly, the ratio of sodium to potassium need not be accurately determined. Thus the correction factor is for practical purposes the same whether the ratio is 2:1 or 2·2:1. Therefore it hardly affects the accuracy whether the found potassium value or the actual value is used to determine the sodium–potassium ratio. Secondly, when the calibration curve (transmission energy *versus* concentration) is linear, the correction factor can be applied directly to the found concentration, instead of to the found transmission energy as in the example described above.

The second method of overcoming sodium interference in potassium estimations is to add an excess of sodium to the test sample and to the potassium standards, so that the interference is constant and at a maximum, as can be predicted from the flattening-out of the interference curve. This method is favoured by Domingo and Klyne (1949). It has the disadvantage that sodium and potassium estimations cannot so readily be performed on the same sample, and this may be an important consideration in plasma analysis. It is a useful method in urinary analysis and will be discussed further in the section dealing with this subject.

The third method of overcoming the interference of sodium in potassium estimations is to use a standard solution which approximates to the test solution in the ratio of the interfering and test ions. This is the method we use in estimating potassium in plasma, as will be discussed in a later section.

The Interference of Potassium in Sodium Estimations.

Figure VIII shows the effect of adding up to 16 milligrammes *per centum* of potassium to 0·5 milligramme *per centum* of sodium. An increase in the emission energy of the sodium ions is shown, but the curve tends to flatten out at much lower concentrations of potassium than is the case with sodium interference in potassium estimations. Thus the interference is practically at a maximum when the ratio of potassium to sodium in milligrammes *per centum* is 6:1 (millimolar ratio 3·5:1). The interference of potassium in sodium estimations is the same at 14 and at 10 inches of water oxygen pressure, so that it does not show the same sensitivity to alterations in the flame temperature as is seen in sodium interference in potassium estimations. Thus the interference curve with the high temperature air-acetylene flame (Domingo and Klyne, 1949) resembles that with the oxygen-air flame. The optimum oxygen pressure for sodium estimations is 14 inches of water—hence a much hotter flame is used for sodium compared with potassium analysis. The methods of overcoming potassium interference in sodium estimation are similar to those described in dealing with sodium interference in potassium estimation.

Phosphate Interference in Sodium and Potassium Estimation.

Phosphate interference was given considerable prominence in the earlier literature, since with the low-temperature air-gas flame phosphate seemed greatly to depress both sodium and potassium emissions (Crismon, 1948; Parkes, Johnston and Lykken, 1948). Shapiro and Hoagland (1948), using the same flame temperature but lower concentrations of sodium and potassium, were unable to demonstrate this interference effect. With the higher temperature oxygen-gas flame we found that the spectral emission energy of sodium and potassium (as chlorides) was the same as that of the corresponding monobasic and dibasic phosphate salts. This agrees with the findings of Domingo and Klyne (1949). When increasing amounts of potassium phosphate (as either the monobasic or dibasic salt) were added to a constant amount of sodium chloride, the potassium interferenee was identical with that produced by a potassium chloride solution (Figure VIII). Hence no interference by phosphate in sodium estimations could be demonstrated. However, when increasing amounts of sodium phosphate were added to a constant amount of potassium chloride so that the ratio of phosphate to potassium (in millimols) was greater than one, significant depression of the potassium emission

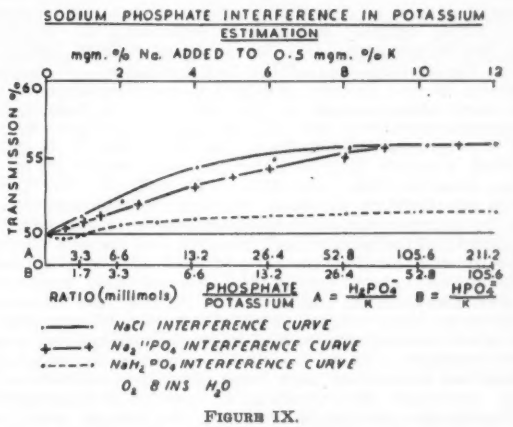

FIGURE IX.

energy occurred (Figure IX). This effect was most pronounced with the monobasic phosphate salt (NaH_2PO_4), and at its maximum caused approximately an 8% depression of the expected potassium emission energy. With the dibasic phosphate salt (Na_2HPO_4) the phosphate depression was considerably less, being approximately 2% at its maximum, and the phosphate depression disappeared at high concentrations of the dibasic salt. The difference in the behaviour of phosphate in sodium and potassium analyses is possibly due to the lower flame temperature used in the latter analysis. The implications of these observations on phosphate interference in the potassium spectral emission energy will be discussed in the sections dealing with potassium estimation in biological fluids.

Calcium Interference.

Calcium interference has been referred to in the general discussion on interference above. Calcium does not directly enhance or depress either sodium or potassium emission energy.

Interference by Other Substances.

Organic acids (oxalic, citric, acetic), ammonia, urea, glucose and lipides (cholesterol), when present in concentrations approximately twice those which could be expected in biological material at dilutions corresponding to those used in the analyses, produced no demonstrable effect upon the emission of sodium and potassium ions. Protein, apart from the viscosity factor which will be discussed later, also had no direct effect upon the sodium and potassium emission. Consequently these substances do not interfere in the estimation of sodium and potassium in clinical work.

TABLE I.

Recoveries of Sodium Added to Plasma (Milligrammes of Sodium per 100 Millilitres).

Sample Number.	Plasma Concentration. *A.*	Added Sodium. *B.*	Calculated. *A+B.*	Found. *C.*	Error. (Milligrammes per 100 Millilitres; $C-(A+B)$.)	Percentage Error. $\left(\frac{C-(A+B)}{A+B}\times 100\right)$
I..	330	250	580	595	+15	+2
	330	200	530	530	0	0
	330	125	455	445	−10	−2
	330	50	380	375	−5	−1
	330	25	355	355	0	0
II	160	250	410	400	−10	−2
III..	328	200	528	540	+12	+2·5
IV..	172	250	422	412	−10	−2
	172	125	297	290	−7	−2

Internal Standard Flame Photometry.

The use of internal standards is a well-established practice in emission spectrography. The principle of the method applied to flame photometry by Berry, Chappell and Barnes (1946) is as follows. An element is selected which does not occur in the test material, and whose excitation characteristics are similar to those of the test element, but whose spectral emission is sufficiently far removed on the wave-length scale for it to be readily separated from the spectral line of the test substance. A constant amount of this internal standard element is added to the standard solutions and to the unknown. A dual optical system is employed, and upon excitation the light emitted by the internal standard and the test element is determined. Actually light intensity ratios are measured, rather than absolute light intensities. Theoretically any factor such as alteration in flame temperature, viscosity effects or the interference of foreign substances in the solution, affects the internal standard element and the test element equally, and therefore the ratio of light intensities obtained is constant regardless of the experimental conditions. Berry, Chappell and Barnes (1946) found that with their low-temperature air-gas flame photometer lithium was a suitable internal standard element for sodium and potassium analyses. With the higher temperature oxygen-gas flame we found that there were significant differences in the excitation characteristics of sodium and potassium. Consequently it could be predicted that lithium would not be a suitable internal standard element for both potassium and sodium analyses. On investigation it was found that lithium resembled potassium, rather than sodium, in its excitation characteristics. However, we were not able to demonstrate any advantage in the use of an internal standard method compared with the simpler procedure. Lithium recovery experiments were used, however, in order to investigate possible differences in viscosity between the test sample and the standard solutions. Thus known amounts of lithium (as analytical reagent lithium sulphate) were added to both the test sample and the standards. If the viscosity of the test solution was significantly greater than the standard, its rate of aspiration was less than that of the standard, and the found lithium value was less than the lithium value of the standard. We will refer to this subject again in dealing with potassium estimations in plasma.

Sodium and Potassium Estimations in Biological Fluids.

Sodium Estimations in Plasma.

Sodium estimations in plasma or serum are carried out as follows. Sodium chloride solutions containing 1·0, 0·8, 0·6, and 0·4 milligrammes *per centum* of sodium in distilled water are prepared as standards. A one millilitre aliquot of heparinized plasma or of serum is preferred, but accurate results can be obtained by the use of 0·2 millilitre samples. In normal plasma a 400-fold dilution gives a solution containing approximately 0·85 milligramme of sodium per 100 millilitres of solution, corresponding to an original concentration of 340 milligrammes of sodium per 100 millilitres of plasma. This dilution gives a reading of about 88% transmission on the transmission scale (Figure V), which is well within the accurate range of the instrument. The range of plasma sodium we have encountered in clinical work varies between 240 and 460 milligrammes of sodium per 100 millilitres, although the extreme limits are rarely seen. For these grossly abnormal plasma samples the 400-fold dilution is not satisfactory, but gives an approximate value from which the correct dilutions can be readily determined. At these high dilutions interference due to viscosity or to the presence of foreign substances is negligible, and consequently the estimation of plasma sodium by the flame photometer is accurate and rapid and can be carried out on a small sample (0·2 millilitre). When known amounts of sodium (as sodium chloride) are added to plasma, the found sodium values are within 2·5% of the calculated values (Table I).

Potassium Estimations in Plasma.

Potassium estimations in plasma or serum are made as follows. The Beckman flame photometer can be used to measure accurately the potassium concentration in solutions containing as little as 0·25 milligramme of potassium per 100 millilitres. This is a much smaller potassium concentration than can be determined by the lower tempera-

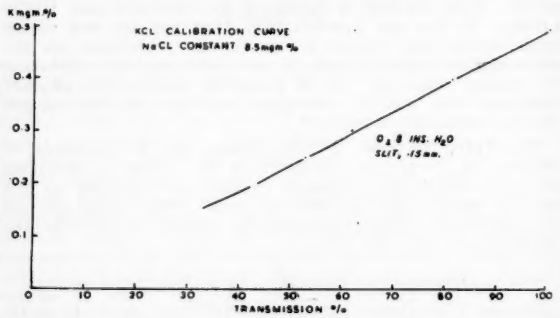

FIGURE X.

ture, air-gas types of instrument. Normal plasma or serum diluted 40 times gives a potassium concentration of about 0·45 milligramme per 100 millilitres, which is well within the accurate range of the instrument. The plasma or serum is prepared for analysis by diluting an aliquot 40-fold with distilled water.

In a 40-fold dilution of plasma the sodium concentration is usually about 8·5 milligrammes per 100 millilitres, if it is assumed that the plasma sodium concentration is 340 milligrammes per 100 millilitres. Consequently the sodium interference in the potassium estimation must be considered. The potassium standards therefore are made up to contain from 1·0 to 0·2 milligramme *per centum* of potassium and a constant amount of 8·50 milligrammes *per centum* of sodium, analytical reagent chlorides being used. Figure X is a calibration curve with these potassium standards from 0·5 to 0·2 milligramme *per centum*. Over this range the curve is practically linear. As a routine measure the 0·5 milligramme *per centum* potassium standard is set to give 100% transmission. Plasma potassium values of 20 milligrammes per 100 millilitres or less can thus be read. Occasionally plasma values greater than this are encountered, and for these the higher potassium standards are used.

TABLE II.

Recoveries of Potassium Added to Plasma (Milligrammes of Potassium per 100 Millilitres).

Sample Number.	Plasma Concentration. *A.*	Potassium Added. *B.*	Calculated. *A+B.*	Found. *C.*	Error. (Milligrammes per 100 Millilitres; $C-(A+B)$.)	Percentage Error. $\left(\frac{C-(A+B)}{A+B}\times 100\right)$
I..	14·7	4·8	19·5	19·7	+0·2	+1
	14·7	4·0	18·7	18·8	+0·1	+0·5
	14·7	2·5	17·2	17·6	+0·4	+2
II..	14·0	4·8	18·8	18·6	−0·2	−1
	14·0	4·0	18·0	17·8	−0·2	−1
	14·0	2·5	16·5	16·5	±0	0
III..	17·4	2·0	19·4	19·6	+0·2	+1
	17·4	10·0	27·4	26·8	−0·6	−2

It will be seen from Figure VII that at the lower flame temperature alterations of the sodium–potassium ratio from 8:1 to 20:1 produce approximately a 3% difference in the potassium transmission value. Clinically ratios higher than 20:1 are not infrequently encountered, but at these ratios the level of sodium interference is for practical purposes the same as that at a ratio of 17:1. We have never encountered in plasma a sodium–potassium ratio as low as 8:1. Consequently for practical clinical purposes the potassium standards made up with a constant amount of 8·5 milligrammes *per centum* of potassium are suitable for the estimation of plasma potassium, despite the wide variations in the concentrations of plasma sodium encountered in clinical cases. Even this small error (maximum 3%) can be corrected by using the interference curve.

The method of Domingo and Klyne (1949) for overcoming sodium interference could also be used. The aliquot of plasma could be diluted with a solution containing 10 milligrammes *per centum* of sodium. The final

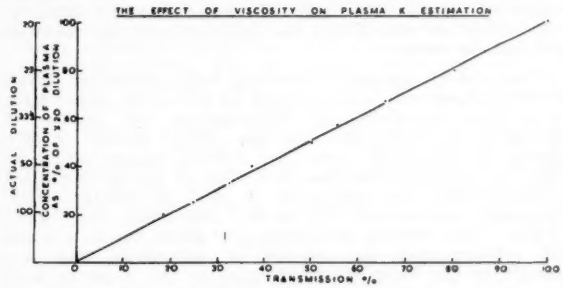
THE EFFECT OF VISCOSITY ON PLASMA K ESTIMATION
ACTUAL DILUTION
CONCENTRATION OF PLASMA AS % OF 1:20 DILUTION
TRANSMISSION %

FIGURE XI.

sodium–potassium ratio would then always be greater than 18:1 whatever the initial plasma ratio was. Hence sodium interference would always be at a maximum. The potassium standards would contain 18·5 milligrammes *per centum* of sodium. The slightly greater accuracy of this method is offset by the fact that it rather complicates the procedure when sodium and potassium analyses are required on the same sample. With the method we have described, both sodium and potassium analyses can be readily made on one aliquot of plasma, which may be as little as 0·2 millilitre. From the 40-fold dilution used for potassium, an aliquot can be taken, diluted a further ten times and used for the sodium analysis. We have found this to be a very worth-while feature of the method.

Interference due to Viscosity.

Since a one in 40 dilution of plasma contains considerable quantities of plasma protein, it was important to determine whether this seriously reduced the rate of aspiration and atomization of the plasma compared with the standard, which was an aqueous solution containing electrolytes only. Mosher, Boyle, Bird, Jacobson, Batchelor, Iseri and Myers (1949), using gelatin to simulate the plasma proteins, demonstrated a pronounced viscosity effect due to the protein, and stated that it was necessary to add gelatin to the standard solutions. We were unable to confirm the presence of a significant viscosity difference in a 40-fold dilution of plasma compared with the aqueous standards. The problem was investigated in five ways.

1. Plasma potassium estimations gave the same results on ashed and unashed specimens. The ashing procedure used was as follows.

Three millilitre aliquots of plasma were evaporated to dryness at 100° C. in silica crucibles. The dried plasma was then gently charred by cautious heating over a Bunsen flame. The specimens were then heated to 440° C. for sixteen hours in a muffle furnace. To the whitish ash three millilitres of 0·2 N hydrochloric acid were added, and then 117 millilitres of distilled water were added to make a final volume of 120 millilitres. This corresponds to a 40-fold dilution of the original whole plasma. Triplicate analyses agreed within 1%.

2. A specimen of plasma was diluted 20, 25, 30, 35, 40, 50, 60, 80 and 100 times. With the 20-fold dilution set to read 100% transmission, the potassium values for the remaining samples fell accurately upon a straight line, which could not have been the case had a decreasing viscosity effect been operating (Figure XI). However, when several samples of the one in 20 dilution were read in succession, the capillary tended to "block", owing presumably to the precipitated globulins "sticking" to the capillary wall. This "blocking" did not occur with the one in 40 dilution, which was therefore selected for routine use.

3. Four millilitre aliquots of plasma diluted 1:40, and of aqueous potassium standard, were separately aspirated into the flame photometer for three minutes. The volume of each solution aspirated per unit of time, calculated from the loss of weight of the samples, was the same, within the limits (2%) of experimental error.

4. Lithium sulphate was added to plasma samples and to aqueous standards, so that the amounts of lithium in the standard and in the diluted plasma were 1·0, 0·50, 0·40 and 0·20 milligramme per 100 millilitres respectively. The recovery of lithium in the plasma was virtually 100% (± 1%). Therefore, there could not be a significant viscosity difference between the diluted plasma and the aqueous standard.

5. Known amounts of potassium were added to plasma. The recovery experiments were satisfactory, the errors being within 2% (Table II).

It was therefore concluded that with a one in 40 dilution of plasma or serum, viscosity effects due to organic plasma constituents were negligible. The difference between our results and those reported by Mosher *et alii* could possibly be due to a smaller bore capillary in the aspirator used by Mosher *et alii*.

The use of a "wetting" agent (0·04% "Sterox SE"—Monsanto Chemical Company) to reduce capillarity effects in the aspirator, as recommended by Weichselbaum and Varney (1949), was not found to improve the accuracy or precision of the analysis.

Table III shows the results of sodium and potassium analyses in the serum and plasma of 20 normal subjects. The blood was withdrawn by venepuncture with the usual precautions to prevent venous stasis or hæmolysis. Portion of the blood was heparinized to prevent clotting, and the remainder was allowed to clot at 37° C. for twenty minutes. At the end of this time both specimens were centrifuged to obtain the plasma and serum. The sodium analyses in

corresponding serum and plasma are virtually the same. The values correspond with those usually accepted as the normal range. Potassium analyses show a significantly lower result in plasma than in serum. Further investigations into the normal range of plasma and serum potassium, and into the effects upon the potassium concentration of such factors as the time that elapses, and the temperature, before the plasma or serum is separated from the cells, are being carried out and will be reported separately.

Table IV shows a comparison of the sodium and potassium estimations in plasma by the present method of flame photometry and the chemical methods previously used in this laboratory. The chemical method used for sodium analysis was a colorimetric uranyl zinc acetate procedure (Peters and Van Slyke, 1932). The chemical potassium estimations were performed by a cobalti-nitrite method modified by Stratmann (1949).

Urinary Sodium and Potassium Estimations.

The sodium and potassium standards for estimation of these minerals in urine are solutions of sodium and potassium chloride containing 1·0, 0·8, 0·6 and 0·4 milligrammes *per centum* of sodium and potassium respectively.

TABLE III.
Sodium and Potassium Values in 20 Specimens of Normal Serum and Plasma.

Test Fluid.	Sodium (Milligrammes per 100 Millilitres).		Potassium (Milligrammes per 100 Millilitres).	
	Mean.	Range.	Mean.	Range.
Serum	332	320 to 348	17·5	14·6 to 20·0
Plasma	330	318 to 348	17·1	14·1 to 20·0

The urine is diluted to 300 times its original volume. The content of sodium and potassium in urine can usually be read at this dilution. If this dilution is unsatisfactory, the approximate concentration can usually be obtained and the urine rediluted accordingly.

Interference in Sodium Estimation.—At these high dilutions viscosity effects due to protein are negligible. Urinary sodium concentrations may be very low (one to two millimols) in the presence of high concentrations of potassium, phosphate, calcium, ammonium, urea and glucose. It has been shown that the last five factors produce negligible interference. Potassium interference, unless recognized, could cause the sodium estimation to be as much as 11% too high (Figure VIII). In practice, since the potassium concentration can be readily determined, a satisfactory correction for clinical purposes can be made by reference to an interference curve such as Figure VIII. Table V shows the results of a typical experiment carried out to determine the accuracy of sodium estimations in urine. A urine sample was selected which contained an extremely small amount of sodium and a relatively great excess of potassium. The sodium and potassium were estimated in the usual way. Then, to correct for the potassium interference in this initial sodium estimation, standards were made up containing a potassium–sodium ratio of 180 to 1. By the use of these standards, the actual sodium concentration (A) was found to be 0·80 milligramme per 100 millilitres. The potassium value (B), which was not subject to any sodium interference, was 144 milligrammes per 100 millilitres. Small errors in either of these values do not affect the subsequent discussion. To aliquots of this urine known amounts of sodium (as sodium chloride) were added—the added amounts are shown in parentheses in the second column of Table V. To some of these samples known amounts of potassium (as potassium chloride) were added. Thus eight samples were prepared in which the actual sodium concentration (A) and the actual potassium concentration (B) were accurately known, and the potassium–sodium ratios were a fair representation of the ratios encountered in clinical cases. Then, by the use of the pure sodium chloride standards, the apparent sodium concentrations (C) in the eight samples were determined. The difference between the apparent sodium value (C) and the actual value (A) (sixth and seventh columns, Table V) shows the magnitude of the errors when the estimation is not corrected for interference. From the potassium–sodium ratio and the known interference curve (Figure VIII) a correction factor $X\%$ was derived, as described in the section dealing with interference. By the use of this factor, the corrected sodium value (Z) was obtained from the formula $Z = \frac{100C}{100 + X}$. The difference between the actual sodium value (A) and the corrected sodium value (Z) is shown in the last two columns of Table V. The errors are well within the limits of accuracy required for clinical work.

The second method of dealing with potassium interference in sodium estimations is to dilute the urine with a solution containing 20 milligrammes *per centum* of potassium as potassium chloride. Since sodium is estimated at 1·0 milligramme *per centum* concentration or less, the ratio of potassium to sodium in the urine diluted appropriately will always be 20 to 1 or greater. Consequently interference will be at a maximum (see Figure VIII). The sodium standards are made up to contain 20 milligrammes *per centum* of potassium, and consequently the level of interference is the same in both standards and the test samples. This is the method of choice when only sodium estimations are required. We

TABLE IV.
Comparison of the Results of Sodium and Potassium Estimations in Plasma by Flame Photometry and by Chemical Methods.

Sample Number.	Potassium (Milligrammes per 100 Millilitres).				Sodium (Milligrammes per 100 Millilitres).			
	Chemical Method.[1] A.	Flame Photometer. B.	Difference. (Milligrammes per 100 Millilitres; $A-B$.)	Percentage Difference. $\left(\frac{A-B}{A}\times 100\right)$	Chemical Method.[2] A.	Flame Photometer. B.	Difference. (Milligrammes per 100 Millilitres; $A-B$.)	Percentage Difference. $\left(\frac{A-B}{A}\times 100\right)$
I	14·3	14·4	−0·1	−0·7	360	350	+10	+2·7
II	14·3	14·7	−0·4	−3	380	377	+3	+0·9
III	14·3	13·2	+1·1	+7	356	377	−21	−6
IV	14·0	14·0	±0	±0	380	391	−11	−3
V	12·0	12·4	−0·4	−3	322	340	−18	−5·6
VI	20·6	19·5	+1·1	+5				
VII	15·0	14·2	+0·8	+5				
VIII	14·6	14·0	+0·6	+4				

[1] Cobalti-nitrite method (Stratmann, 1949).
[2] Zinc uranyl acetate method (Peters and Van Slyke, 1932).

TABLE V.
Sodium Estimations in Urine and the Effect of Potassium Interference.

Sample Number.	Actual Sodium (Milligrammes per 100 Millilitres.) *A.*	Actual Potassium. (Milligrammes per 100 Millilitres.) *B.*	Potassium-Sodium Ratio. *B* : *A.*	Apparent Sodium. (Milligrammes per 100 Millilitres.) *C.*	Error. (Milligrammes per 100 Millilitres.) $C-A$.	Percentage Error. $\frac{C-A}{A}\times 100$	Correction Factor *X per Centum.*	Corrected Sodium $\frac{100C}{100+X}=Z$ Milligrammes per 100 Millilitres.	Error. (Milligrammes per 100 Millilitres.) $A-Z$.	Error. (Milligrammes *per Centum.* $\frac{A-Z}{A}\times 100$)
I ..	0·80	144	180 : 1	—	—	—	—	—	—	—
II ..	50·8 (+50)	144	3 : 1	53·5	+2·7	+5·3	8	49·5	−1·3	−2·6
III ..	50·8 (+50)	544	11 : 1	56·0	+5·2	+10·2	11	50·5	−0·3	−0·6
IV ..	150·8 (+150)	144	1 : 1	160·1	+9·3	+6·2	4·5	153·0	+2·2	+1·4
V ..	150·8 (+150)	1144	8 : 1	168·0	+17·2	+11·4	11	151·3	+0·5	+0·3
VI ..	150·8 (+150)	1644	11 : 1	170·0	+19·2	+12·8	11	153·1	+2·3	+1·5
VII ..	400·8 (+400)	144	1 : 3	407·5	+6·7	+1·7	1·5	401·4	+0·6	+0·2
VIII ..	400·8 (+400)	1144	3 : 1	432·5	+31·7	+8	8	400·5	−0·3	−0·1

have not adopted it as a routine measure, because we have required sodium and potassium estimations in most of our urinary samples. The first method outlined considerably reduces the number of laboratory manipulations when both cations are being estimated, without a significant decrease in accuracy.

Interference in Potassium Estimations.—Substances in urine which may interfere with potassium estimations are sodium, which enhances the potassium emission, and phosphate, which may depress it. Sodium interference is corrected by using the interference curve, or by diluting the urine with a solution containing 20 milligrammes *per centum* of sodium, the potassium standards in this case also containing 20 milligrammes *per centum* of sodium. Table VI shows the results of potassium estimations in urinary samples in which the actual potassium and sodium values were known. The interference curve was used to correct the potassium value. The accuracy of the results is well within the limits required for clinical work.

In discussing phosphate interference in potassium estimations, it was pointed out that phosphate depresses the potassium emission only when the phosphate–potassium ratio (in millimols) is greater than one. It was also shown that the phosphate depression of the potassium emission was much less when the phosphate was present as the dibasic sodium salt compared with the monobasic salt. Usually in urine the phosphate–potassium ratio is less than one, just as it is in the intracellular fluid. Hence phosphate interference is usually negligible. When urinary phosphate excretion is high, the urinary potassium excretion is usually high also. Occasionally, however, the phosphate–potassium ratio is greater than one. In alkaline urine the phosphate is present largely as the dibasic sodium salt or the potassium salt, or as a mixture of both. The highest phosphate–potassium ratio (in millimols) we have found in alkaline urine was 6:1. This has occurred only once in several hundred analyses. The phosphate was present largely as sodium monohydrogen phosphate, and from Figure IX it can be seen that this would cause only about a 2% depression of the potassium emission. In acid urine the highest phosphate–potassium ratio we have found is 3:1. At this ratio the phosphate causes a 3% to 4% depression of the potassium emission. For most clinical purposes this degree of error in potassium estimations in urine is of little importance. However, phosphate interference can be readily overcome. If powdered analytical reagent calcium hydroxide is added to the urine (approximately 50 milligrammes of calcium

TABLE VI.
Potassium Estimations in Urine and the Effect of Sodium Interference.

Sample Number.	Actual Potassium. (Milligrammes per 100 Millilitres.) *A.*	Actual Sodium. (Milligrammes per 100 Millilitres.) *B.*	Sodium-Potassium Ratio *B* : *A.*	Apparent Potassium. (Milligrammes per 100 Millilitres.) *C.*	Error. (Milligrammes per 100 Millilitres.) $C-A$.	Error. (Milligrammes *per Centum.* $\frac{C-A}{A}\times 100$	Correction Factor *X per Centum.*	Corrected Potassium $\frac{100C}{100+X}=Z$ Milligrammes per 100 Millilitres.	Error. (Milligrammes per 100 Millilitres.) $A-Z$.	Error. (Milligrammes *per Centum.*) $\frac{A-Z}{A}\times 100$
I ..	144·0	0·80	1 : 180	144·0	—	—	—	—	—	—
II ..	144·0	50	1 : 3	146·0	+2·0	+1·4	0·5	145·2	+1·2	+0·8
III ..	144·0	150	1 : 1	147·9	+3·9	+2·7	1·5	145·7	+1·8	+1·2
IV ..	144·0	300	2 : 1	150·0	+6·0	+4·2	3·0	145·6	+1·6	+1·1
V ..	144·0	600	4 : 1	152·2	+8·2	+5·5	5·5	144·0	±0	±0
VI ..	144·0	1200	8 : 1	155·8	+11·8	+8·2	8·5	143·7	−0·3	−0·2
VII ..	144·0	3000	20 : 1	165·0	+21	+14·6	11·0	148·6	+4·6	+3·1
VIII ..	169·0 (+25)	0·80	1 : 200	170·0	+1·0	+0·6	—	—	—	—
IX ..	194·0 (+50)	0·80	1 : 250	195·0	+1·0	+0·5	—	—	—	—
X ..	294·0 (+150)	0·80	1 : 350	297·1	+3·1	+1·0	—	—	—	—
XI ..	194·0 (+50)	300	1·5 : 1	200·0	+6·0	+3·0	2·5	195·0	+1·0	+0·5
XII ..	194·0 (+50)	600	3 : 1	205·8	+11·8	+5·9	4·0	198·0	+4·0	+2·0
XIII ..	194·0 (+50)	1200	6 : 1	212·0	+18·0	+9·0	7·0	198·0	+4·0	+2·0

hydroxide to 10 millilitres of urine), the phosphates are precipitated as the insoluble calcium salts. The urine is filtered and the potassium estimation is carried out in the usual way. Recovery experiments on urine to which known amounts of potassium and sodium phosphate were added showed that the precipitation of the phosphate by calcium overcame the phosphate interference without detectable loss of potassium by coprecipitation, nor did the added calcium itself interfere with the potassium estimation.

Domingo and Klyne (1949) obtained considerably lower potassium concentrations in ashed urine, compared with the values obtained with unashed urine. The lower photometer values generally agreed with the results obtained by the chemical method of Abul-Fadl on ashed urine. They were unable to advance any reason for this finding. Hald (1947), using an air-gas flame, found good agreement between the chemical and photometer results, as did Weichselbaum and Varney (1949), using a propane-oxygen flame. We were unable to demonstrate any difference in the urinary potassium estimations on unashed or ashed urine. Table VII shows the results of a typical experiment. The ashing procedure used was similar to that described by Domingo and Klyne. In addition, recovery of added potassium was the same in both cases.

TABLE VII.

Potassium Estimations on Unashed and Ashed Urine. (Milligrammes of Potassium per 100 Millilitres.)

Sample Number.	Unashed.	Ashed.
*A*1	300	303
*A*2	303	301
A+53 milligrammes of potassium per 100 millilitres	350	351

CONCLUSION.

The features of the flame photometer method for sodium and potassium analysis which make it an important technique in clinical biochemistry are its speed, accuracy and reliability, and the small amount of sample it requires. Many attempts have been made to "speed up" the chemical methods, particularly for sodium analysis. The sodium method of Goldzieher and Stone (1949) seems to have been the most successful. But even this method is time-consuming compared with flame photometry. When large numbers of analyses have to be made, the advantages of the flame photometer method become even more obvious. There are no rapid chemical methods for potassium analysis. If modern knowledge of the role of the potassium ion in disease is to be applied clinically, some form of flame photometer to carry out potassium analyses becomes necessary.

The only disadvantage of the flame photometer method is the initial cost of the apparatus. However, the need for such a method in clinical biochemistry is great. The economic factor should not be allowed to prevent its adoption as a routine method. It can be recognized also that the versatility and accuracy of the Beckman instrument are actually greater than are required for routine clinical work. There is therefore no reason why an instrument suitable for clinical purposes could not be produced at a considerably lower cost than the instrument described in this paper. We look forward confidently to the time when flame photometry will become a widely used technique, and to the more vigorous participation of the clinical biochemist in the treatment of the severely ill patient.

ACKNOWLEDGEMENTS.

The advice and unfailing encouragement of Professor R. D. Wright are gratefully acknowledged. The Beckman flame spectrophotometer used in this work was a gift of the Rockefeller Foundation. The figures and graphs were drawn by the Department of Visual Aids, University of Melbourne.

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THE INFLUENCE OF MATERNAL MEASLES (MORBILLI) ON THE UNBORN CHILD.

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IN 1941 Gregg showed for the first time that a disease (rubella) in a pregnant woman may be associated with congenital abnormalities in her offspring. His findings have been supported and elaborated by numerous workers, and it is now known (Wesselhoeft, 1947, 1949; Swan, 1949) that this disease may have no effect on the offspring or may produce abnormalities, stillbirth, abortion or possibly congenital rubella (Corlett, 1902). The stage of pregnancy at which the maternal disease occurs is an important factor in determining whether ill-effects are likely to result. In those cases in which the mothers suffered from rubella during the first trimester (corresponding approximately to the organogenetic period of the embryo), a large proportion of the offspring were congenitally defective, whereas very few abnormalities were associated with maternal rubella occurring later in pregnancy.

It has been suggested, so far on very little evidence, that other maternal virus diseases occurring in the early part of pregnancy may also be a cause of congenital abnormalities. The present investigation, dealing only with morbilli, considers the evidence indicating that this disease in a pregnant woman may produce harmful effects in her offspring. A brief review of the literature is followed by a report of cases occurring during a recent measles epidemic in South Australia.

Survey of the Literature.

There is no lack of reports indicating that maternal measles during pregnancy may influence the child *in utero* (Table I). Thus Düttel, in 1702, was aware of the transmission of measles across the placenta, and Wilson (1800) mentions that the fœtus may "receive the measles from the mother". Ballantyne (1902) collected about 20 cases of congenital measles from the literature, and in Nouvat's (1904) 84 cases of morbilli in pregnant women, placental transmission occurred 21 times. More recently the occurrence of congenital measles has been reported by Reuss (1914), by Canelli (1929) and by Kohn (1933). In some infants the congenitally acquired infection proved fatal, but in the majority the disease was not severe. There is general agreement that the fœtal disease was in much the same stage as the maternal; this indicates that mother and child were probably both invaded by the virus at about the same time. One of Ballantyne's cases is of interest, in that a mother suffering from measles aborted during the sixth month of pregnancy and the fœtus showed a typical measles rash; this indicates that the placenta may be permeable to the virus at least as early as the sixth month.

Maternal morbilli may also bring about a termination of pregnancy. Reports differ on the frequency with which this may occur. Thus, Lynch (1932) states that "the fetus rarely lives"; Greenhill (1933) in his review reported an abortion rate of 45% to 76%; Swan *et alii* (1946) reported 18 cases of maternal measles during pregnancy with only one abortion; Heberden (cited by Wilson, 1800) noted no harmful effect on the offspring. Stillbirth in association with measles during gestation seems very rare, and only one case could be found (Swan, 1948).

Cases of congenital defects in association with maternal morbilli are few, and all have been reported since Gregg's discovery of the teratogenic action of rubella. Most cases were discovered by the "reverse" method of inquiring into the gestational history of mothers who had given birth to abnormal offspring. Rones (1944) reported such a case following maternal measles in the first trimester. Albaugh (1945) noted two cases, in each of which a congenital heart lesion, bilateral cataract and general slowing of development were present; one mother suffered from measles during the eighth week of pregnancy and the other was exposed to measles during the fourth week. Swan *et alii* (1946) in 18 cases of maternal disease found that three of the offspring had congenital defects (heart disease, heart disease with pyloric stenosis, *genu valgum*); as two of the mothers were infected after the organogenetic period of the embryo, it is unlikely that the maternal disease was the cause of the anomalies in these cases. Dogramaci and Green (1947) reported obstruction of the "right lacrimal duct" in the offspring of a mother who had a "mild" infection during the third month of pregnancy. Grönvall and Selander (1948) also reported a case of congenital defects associated with maternal morbilli during the first trimester. Fox *et alii* (1948) recorded a case of hare-lip, the mother having suffered from measles during the fourth month of pregnancy.

Thus there are recorded in the literature only six cases of congenital abnormality associated with maternal measles (exposure only to this disease in one instance) during the first trimester; obviously with so few cases coincidence cannot be excluded. There are also recorded (Swan *et alii*, 1946) five cases in which normal babies were born to mothers who suffered from measles during the first three months of pregnancy.

Present Investigation.

In 11,000 cases of measles in a recent epidemic in South Australia, there were 250 women of child-bearing age (arbitrarily set at eighteen to forty years). Of these women 128 were listed in the records of the Central Board of Health as "Mrs." and to these was sent the accompanying *questionnaire* (see appendix). Interviews were arranged later when further information was required.

All cases of measles were diagnosed by a medical practitioner, and the date of the infection is taken as that on the official form reporting the case to the health authorities. In the cases of abortion and abnormality also, the diagnosis was made by a doctor, but no specific search for congenital defects was made, so it is possible that some less obvious abnormalities may have escaped notice.

TABLE Ia.

Ill-Effects on the Offspring Associated with Maternal Morbilli During Pregnancy—Cases from the Literature: Congenital Measles.

Source.	Cases.	Remarks.
Düttel (1702) ..	A brief description of congenital rubeola.	—
Wilson (1800) ..	Congenital measles may occur.	—
Ballantyne (1902) ..	20 cases.	—
Nouvat (1904) ..	21 cases.	—
Reuss (1914) ..	? cases.	—
Canelli (1929) ..	? cases.	—
Kohn (1933) ..	8 cases.	Not all these cases proven congenital.

TABLE Ib.

Ill-Effects on the Offspring Associated with Maternal Morbilli During Pregnancy—Cases from the Literature: Interruption of Pregnancy.

Source.	Incidence.	Remarks.
Heberden (cited by Wilson, 1800) ..	Nil.	—
Lynch (1932) review	"Fetus rarely lives."	Percentage not stated.
Greenhill (1933) review	45% to 76%.	—
Swan *et alii* (1946)..	One case in 18.	Abortion occurred 10 days after onset of rash.

TABLE Ic.

Ill-Effects on the Offspring Associated with Maternal Morbilli during Pregnancy—Cases from the Literature: Congenital Abnormalities.

Source.	Stage of Pregnancy during Maternal Infection.	Abnormalities.
Bones (1944) (1 case)	First trimester.	?
Albaugh (1945) (2 cases)	(i) 4 weeks (exposure only).	(i) Congenital heart disease, bilateral cataract, general slowing of development.
	(ii) 8 weeks.	(ii) Same as (i).
Swan *et alii* (1946) (3 cases).	(i) ? 10 to 12 weeks.	(i) Congenital heart disease.
	(ii) 14 weeks.	(ii) Congenital heart disease and pyloric stenosis.
	(iii) 16 weeks.	(iii) *Genu valgum*.
Dogramaci and Green (1947) (1 case).	12 weeks.	Obliteration of "right lacrimal duct".
Grönvall and Selander (1948) (1 case).	First trimester.	?
Fox *et alii* (1948) (1 case)	16 weeks.	Hare-lip.

Results and Discussion.

Eighteen cases of pregnancy complicated by measles were discovered (17 cases in the present epidemic and one case occurring earlier). (See Table II.) There were no maternal deaths, although one mother (Case XVII) was gravely ill with pneumonia; this was the only "complicated" case in the series.

The outstanding feature of the results is that the majority of offspring (12 out of 18) were apparently unaffected by the maternal disease. This supports the findings of Swan *et alii* (1946), who noted ill-effects in only four of their 18 cases.

No cases of congenital measles occurred; but this is not unexpected, as there were no cases of maternal infection during the last week or so of gestation.

Premature termination of pregnancy took place on four occasions. With so few cases there can be no proof of a cause and effect relationship between the maternal measles and the interruption of gestation; but in three of the cases (Cases II, XIII and XVII) it seems probable that such an association exists even though the emptying of the uterus took place rather later than would be expected (namely, in the third, second and second weeks following the diagnosis of the maternal disease). The fourth case (Case XVI) was complicated by severe pneumonia, and this is the likely cause of the abortion. Pneumonia is a rare complication of pregnancy, but it causes abortion in two out of three cases, more especially if the disease occurs late in pregnancy (Greenhill, 1933). In Cases II, XIII and XVII the mothers all stated that the measles made them really ill, and one is tempted to suggest greater severity of maternal disease as a factor in causing the termination of pregnancy. However, it must be noted that there were two other cases (Cases V and XVIII) of "severe" measles infection with no apparent ill-effect on the conceptus. There is no evidence that the stage of pregnancy at which the mother is infected has any bearing on the liability to abortion or miscarriage; the three cases of termination of gestation presumed due to maternal morbilli occurred during the seventh, twenty-fourth and thirty-second weeks.

The incidence of interruption of pregnancy in the present series (and in the cases of Swan *et alii*, 1946) does not bear out the high rate of abortion reported by other authors (Lynch, 1932; Greenhill, 1933). Possible explanations of this discrepancy are the milder nature of the maternal infection and the fewer complications present in the more recently reported cases.

It has been suggested that a possible reason why maternal rubella frequently causes congenital defects, whilst other virus diseases do not, is that the milder rubella infection "maims" the embryo, whereas the more severe diseases (for example, morbilli) are lethal. This again is not borne out by the present finding of only three terminations of pregnancy in 18 cases of maternal morbilli.

With regard to congenital abnormality, there were two cases (Case III, mongoloid child, and Case VI, partial deafness) associated with maternal morbilli occurring during the fifth and eighth weeks of gestation. It has been shown both in rubella infection and in animal experiments (Warkany, 1947) that the time of greatest susceptibility of an embryo to a teratogenic agent is during the stage of laying down of the various organs (this organogenetic period in humans extends approximately from the fourth to the tenth week of pregnancy). After this period congenital defects are unlikely to arise. In the present series there were six cases (Cases I to VII), excluding the case of abortion (Case II), of maternal infection during the first trimester of pregnancy: four of the offspring escaped with no apparent abnormality. In the series of Swan *et alii* (1946) there were five similar examples of maternal morbilli during the first trimester with normal offspring resulting.

Thus there are nine cases in which normal offspring were born subsequent to maternal measles infection during (approximately) the organogenetic period. On the other hand, there are seven reported cases of congenital anomalies occurring from infection during the same period. Such a comparison is not a fair one, because, with the exception of the present series and that of Swan *et alii* (1946), the other cases of malformation seem to have been discovered by the method of inquiring into the pregnancy history of mothers who have given birth to abnormal offspring. This method obviously can give no idea of the incidence of abnormalities following maternal morbilli, because it entirely disregards normal offspring born subsequent to such maternal infection.

TABLE II.

Measles During Pregnancy: Cases from the Present Investigation.

Identification: Case Number.	Last Menstrual Period (First Day).	Measles Reported.	Duration of Pregnancy.	Severity of the Disease (Mother's Estimate).	Effect on Offspring.
I. Mrs. C.	25/11/48	13/12/48	1 week.	Not severe.	Nil.
II. Mrs. C.	11/10/48	10/11/48	4 weeks.	"Very ill."	Miscarriage three weeks after the onset of measles.
III. Mrs. E.	20/ 4/48	3/ 6/48	5 weeks.	Severe.	Mongoloid type of child.
IV. Mrs. N.	22/ 9/48	8/11/48	6 weeks.	Not severe.	Nil.
V. Mrs. J.	19/ 8/48	18/10/48	8 weeks.	Severe.	Nil.
VI. Mrs. F.	4/ 9/39	30/10/39	8 weeks.	Severe.	Partial deafness first noted when child ten months old. No known genetic or postnatal cause.
VII. Mrs. O.	26/ 9/48	13/12/48	10 weeks.	Not severe.	Nil.
VIII. Mrs. B.	14/ 6/48	30/10/48	14 weeks.	Mild.	Nil.
IX. Mrs. A.	9/ 9/48	8/ 1/49	16 weeks.	Mild.	Nil.
X. Mrs. B.	9/ 5/48	2/ 9/48	17 weeks.	Mild.	Nil.
XI. Mrs. S.	17/ 9/48	4/ 2/49	19 weeks.	Moderate.	Nil.
XII. Mrs. B.	27/ 7/48	31/12/48	21 weeks.	Mild.	Nil.
XIII. Mrs. D.	20/ 5/48	26/10/48	22 weeks.	Severe.	Abortion in second week of disease.
XIV. Mrs. B.	20/ 7/48	31/12/48	22 weeks.	Moderate.	Nil.
XV. Mrs. W.	28/ 7/48	14/ 1/49	23 weeks.	Mild.	Nil.
XVI. Mrs. L.	15/ 7/48	12/ 1/49	25 weeks.	Severe, complicated by pneumonia.	Macerated fœtus delivered seven weeks after onset of measles.
XVII. Mrs. G.	16/ 4/48	2/12/48	30 weeks.	Severe.	Baby one month premature, born in second week following measles attack; baby progressed satisfactorily.
XVIII. Mrs. R.	16/ 4/48	7/12/48	31 weeks.	Not severe.	Nil.

Although it is unwise to attempt to generalize from such a small number of cases, one seems justified in regarding morbilli as in no way comparable in importance to rubella as a teratogenic agent in humans. Indeed, the association of seven cases of congenital defects with measles infection during the first trimester may be merely fortuitous, and many more cases will have to be investigated before coincidence can be excluded. However, the possibility exists that maternal morbilli may be a cause of abnormal offspring in a minority of cases. It has been shown (Swan, 1949) that rubella can cause death or deformity of the child *in utero*, with the emphasis on deformity. It has also been shown in animal investigation (Warkany, 1947) that other teratogenic agents (for example, Röentgen ray irradiation, maternal deficiency of vitamin *A* or B_2 or *D*) may produce death or deformity of the offspring, depending in part on the severity of action of the agent and on the stage of pregnancy at which it acts. As the occurrence of maternal morbilli has been shown to have a lethal effect on the offspring, in some cases, is it not feasible to expect that, under suitable borderline conditions, it would cause deformity rather than death? On present evidence such teratogenic action is at most a rare occurrence, and it will require a study of some hundreds of cases of maternal measles during the organogenetic period before such action can be substantiated or excluded.

As an incidental finding, it was noted that 10 of the 128 mothers questioned, claimed that they had been previously infected with measles. While it is unlikely that these are all authentic cases of reinfection, this seems a greater frequency than would be expected from the fact that a second attack of measles is very rare (Stokes, 1946). In only one of the cases (Case VIII) was the attack of measles during pregnancy stated by the mother to be a second attack.

Summary.

1. The literature concerning measles during pregnancy is briefly reviewed.

2. In 11,000 cases of measles in a recent epidemic in South Australia there were 128 married women of childbearing age; these were investigated by *questionnaire*.

3. Eighteen cases of maternal measles complicating pregnancy were discovered; there were no maternal deaths.

4. Twelve of the offspring were apparently unaffected. Two were born with congenital abnormalities—in both cases the maternal infection occurred during the organogenetic period. The other four pregnancies terminated prematurely; in three cases the measles was the presumed cause; in the other case the attack of measles was complicated by severe pneumonia which was the probable cause of the abortion.

5. The possibility that maternal measles may be a teratogenic agent is discussed.

Acknowledgements.

I am indebted to the chairman and staff of the Central Board of Health, Adelaide, for kindly making available the data on which this investigation is based.

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Appendix.

Questionnaire.

Dear Mrs. ———,

I am a doctor carrying out an investigation to try to find out whether measles infection of a mother during pregnancy has any ill-effects upon her baby. As you are reported to have had measles in , 1949, you can be of great help if you will kindly answer the following questions. All answers will be kept strictly confidential.

(1) Were you pregnant at the time you had the measles? If so, when was your last normal period? (the first day of).
(2) Have you had measles before?
(3) Did the asles upset the pregnancy in any way?
(4) Was the by born at full term?
(5) Was the y abnormal in any way?

Thank you ve much for your assistance in this inquiry.

Yours faithfully,

THE ESTIMATION OF PREGNANEDIOL IN URINE.[1]

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DURING recent years great interest has been shown in the estimation of urinary pregnanediol because of its use in the diagnosis and treatment of threatened abortion. As a pregnancy test, pregnanediol estimations have not proved of sufficient accuracy to replace the Aschheim-Zondek test or the toad test.

Since the amount of pregnanediol in urine is a useful guide to the possibility of abortion, a rapid method of estimation would be of great value. In this laboratory a number of methods have been investigated with a view to selecting for routine clinical work the one possessing the virtues of shortness and accuracy.

The first reliable method for assaying pregnanediol in urine was devised by Venning (1937). After butanol extraction from the urine and purification, sodium pregnanediol glycuronidate was estimated gravimetrically. For years this method was used as the standard for comparison with any new techniques, but it was extremely tedious and time-consuming. Astwood and Jones (1941) suggested a gravimetric estimation of free pregnanediol liberated from sodium pregnanediol glycuronidate in urine by acid hydrolysis, and extraction with toluene.

A new approach to the problem was put forward in the same year by Allen and Viergiver, who suggested a titrimetric method for estimating the glycuronic acid. However, they found that this method invariably gave higher results than other methods owing to the simultaneous estimation of glycuronidates other than those of pregnanediol, and it was if anything more involved and lengthy than the original method. These results and conclusions were confirmed in this laboratory.

Guterman's twenty-four hour qualitative colorimetric method seemed a revolutionary improvement when it was introduced in 1944. Pregnanediol is liberated from sodium pregnanediol glycuronidate by acid hydrolysis of the urine; it is extracted in toluene and is finally estimated by its colour reaction with concentrated sulphuric acid. Guterman suggested using the test for diagnosis of pregnancy as well as for prediction of abortion. In 1948 he extended his method and transformed it into a quantitative technique. Bender (1947) also found the method useful in deciding the treatment of threatened abortion. However, many workers (Morrow and Benua, 1946; Reinhart and Barnes, 1946; Merrivale, 1948) have been unable to reproduce Guterman's excellent results.

In experiments with Guterman's method in this laboratory, difficulty was encountered in the colour reaction with concentrated sulphuric acid. Instead of the expected yellow to orange colour, brownish char effects made the reading of the results impossible. The cause of these interfering effects was finally traced to the toluene, which, although the purest grade available, was found to contain quantities of unsaturated hydrocarbons as well as sulphur derivatives of toluene. In order to eliminate char effects it was found necessary to purify the toluene by twenty to thirty washings in a separating funnel with concentrated sulphuric acid (five millilitres per 100 millilitres of toluene) until the washings were colourless, and then to distil it over sodium hydroxide. With this toluene it was possible to obtain clear colour reactions with Guterman's technique; but the work involved in toluene purification was too great to permit adoption of the method for routine use.

In contrast to the methods of Allen and Viergiver and of Guterman, the method of Sommerville, Gough and Marrian (1947) was found to give reliable duplicate estimations of urinary pregnanediol. However, no result can be obtained for at least three days, one day being allowed for the collection of a twenty-four hour specimen of urine, and a minimum of two days for estimation. Nevertheless, the reliability of the test makes it, with some modifications, the method of choice in this laboratory.

Huber's chromatographic separation of pregnanediol (1947) has also been considered, but satisfactory results could not be obtained in the three cases tested by this method. Goldzieher's suggestion that pregnanediol gives a colour reaction with acetyl chloride and glacial acetic acid (1948) has been investigated and will be referred to later.

The recent publication of Marrian's shortened method (1948), by means of which an estimation could be completed in one day, was of great interest, and an experiment to be described below was planned to test the suitability of the method for routine clinical use.

MARRIAN'S METHOD FOR ESTIMATING URINARY PREGNANEDIOL.

The method is believed to estimate 90% or more of the pregnanediol present when the concentration is greater than about two milligrammes per twenty-four hours.

A twenty-four hour specimen of urine collected with five millilitres of toluene as preservative is made up to 2·5 litres, and duplicate 500 millilitre samples are removed. Each sample is treated as follows.

It is placed in a flask of one litre's capacity, and after the addition of 100 millilitres of toluene is brought to boiling point under a reflux condenser. To the boiling mixture are added down the condenser 50 millilitres of concentrated hydrochloric acid (A.R.) and the boiling is continued for exactly ten minutes. The flask is then rapidly cooled in cold water and the contents are transferred to a separating funnel of 750 millilitres' capacity. After the mixture has been shaken and the urine layer allowed to separate, the latter is run off into the original flask and the layer of toluene and emulsion is filtered with gentle suction through a Whatman number 1 paper on a Buchner filter funnel. The urine layer is then returned to the separating funnel and extracted twice more with 100 millilitre portions of toluene, each toluene and emulsion layer being filtered in succession through the same filter funnel. The combined filtrates are then transferred to a clean separating funnel, and after the small urine layer that separates has been run off, the toluene extract is washed twice with 100 millilitre portions of normal sodium hydroxide solution and twice with 100 millilitre portions of water. The washed toluene

[1] This work was made possible by a grant from the National Health and Medical Research Council of Australia to the Department of Pathology, the Women's Hospital, Melbourne, for the investigation of pregnanediol excretion in pregnancy.

extract is run into a 500 millilitre round-bottomed flask, evaporated nearly to dryness on an electric hotplate, and then taken completely to dryness under reduced pressure in a boiling water-bath.

The dry residue is transferred quantitatively with warm ethanol to a 20 millilitre conical centrifuge tube, and the ethanolic solution is evaporated to dryness in a water-bath under a stream of air. To the residue in the tube are added exactly 4·0 millilitres of ethanol, and the tube is placed in a beaker of water maintained at 75° C. After the mixture has been stirred with a glass rod for one minute to obtain complete solution, 16·0 millilitres of decinormal sodium hydroxide solution are added with stirring dropwise from a burette over three minutes, the last millilitre being used to wash down the stirring rod into the tube. After a further one minute at 75° C., the beaker of water containing the tube is transferred to an incubator at 37° C. and left overnight. Approximately eight to ten milligrammes of "Hyflo Supercel" (Johns-Manville Company, Limited) are added and the mixture is stirred with a glass rod. The rod is washed down into the tube with one millilitre of a 1:4 (volume for volume) ethanol-water mixture, and the tube is then centrifuged for one hour (3500 revolutions per minute; radius of centrifuge head, 15 centimetres). The supernatant solution is finally sucked off from the precipitate with the aid of a fine glass tube attached to a slowly running water-pump.

The second and third precipitations are carried out as described above, except that water instead of sodium hydroxide solution is used, and the incubation periods are reduced for convenience to two hours. No additional filter-aid is added before the centrifugations following the second and third precipitations.

To the final precipitate are added five millilitres of ethanol, and the pregnanediol is dissolved by warming and stirring of the mixture at about 75° C. "Norite" charcoal (about one or two milligrammes) is then added, and the warming is continued for two minutes. The mixture is filtered through a small filter paper (Whatman number 1) into a test tube of one inch diameter, the centrifuge tube and filter being washed three times with two millilitre portions of warm ethanol. The filtrate and washings in the tube are evaporated in a water-bath under a stream of air and the residue is finally dried off, the tube being left in a vacuum desiccator over calcium chloride for several hours.

The colour reaction is carried out with not more than 0·5 milligramme of the finally purified product. If, therefore, the amount of the latter appears on inspection to be in excess of 0·5 milligramme, a suitably sized aliquot portion is removed after solution in a known volume of ethanol. To the dry pregnanediol 10·0 millilitres of concentrated sulphuric acid (A.R.) are added from a burette, and the tube is left in a water-bath at 25° C. for twenty minutes with occasional shaking. The intensity of the yellow colour produced is measured in a "Spekker" photo-electric absorptiometer, a "spectrum violet" number 601 light filter being used.

The absorptiometer readings are interpreted by reference to a calibration curve made with known amounts of pure pregnane-3(α),-20α-diol, varying from 0·1 to 0·5 milligramme. It is advisable to construct a fresh calibration curve for each batch of unknowns.

In order to test the reliability of this method, 13 tests in duplicate were carried out, the carefully purified toluene being used in order to avoid any complications such as were encountered in the Guterman method. The final products were weighed instead of being estimated colorimetrically (as at this stage no standard for colorimetric comparison had been prepared), and excellent duplicate results were obtained in every case (Table I).

Modifications of Marrian's Method.

The next concern was to attempt to shorten this reliable method to some extent without sacrificing accuracy beyond a limit allowable in clinical practice. In order to do this the following points were considered.

Firstly, since the method had been proved to give accurate estimations when purified toluene was used, the effect of using "pure" toluene as supplied in Melbourne was investigated, and also of using once-distilled toluene (excluding all fractions except that boiling at 110° C.).

Secondly, the effect of shortening the time of centrifugation after precipitation of pregnanediol was considered. Each precipitation is followed by an hour's centrifugation at 3500 revolutions per minute, so that in the course of one estimation three hours' centrifugation is involved.

Thirdly, the effect of making only one or two precipitations was tried and the results were compared with the triple precipitation prescribed by Marrian.

Fourthly, it was hoped that application of a colorimetric procedure to the pregnanediol at the first or second precipitation stages might make it possible to eliminate the third, and perhaps even the second, precipitation. Two colour reactions of pregnanediol were considered: (*a*) Goldzieher's reaction, in which the addition of acetyl chloride and glacial acetic acid to pregnanediol gives a yellow colour which may be estimated in a colorimeter; (*b*) Guterman's reaction, in which a yellow colour is produced when concentrated sulphuric acid is added to pregnanediol. In view of previous poor results with Guterman's method, it was considered less likely that satisfactory results would be obtained by this colorimetric procedure.

Procedure.

In an attempt to assess the effect of these modifications, the following experiment was carried out.

A composite specimen of urine from pregnant women was collected and fourteen 250 millilitre volumes were treated in the following ways.

1. Four samples were extracted with purified toluene; two of these samples (*A*1 and *A*2) were carried through the complete Marrian method, and served as standards. A third sample, *A*3, was precipitated only twice, while the fourth, *A*4, was precipitated once only. All other procedures were the same as those applied to *A*1 and *A*2. The products, dried *in vacuo* over calcium chloride, were weighed, and later subjected to the Goldzieher colorimetric estimation at the same time as the following ten samples.

TABLE I.
Duplicate Assays Made with the Original Marrian Method.

Test Number.	Duplicates. (Milligrammes per One-fifth Twenty-four-Hour Specimen.)	
77	11·7	11·5
80	4·3	5·7
83	4·0	4·4
84	5·3	4·3
86	14·5	14·8
87	2·9	2·5
89	1·0	0·9
91	1·9	1·3
92	0·9	1·1
93	0·8	0·8
95	1·4	1·8
96	0	0
97	2·6	2·8

2. Two samples (*B*1 and *B*2) were hydrolysed and extracted as above, and precipitated three times; however, after the first precipitation the time of centrifuging at 3500 revolutions per minute was shortened to thirty minutes, and after the second and third precipitations to twenty minutes. The final products were weighed and estimated colorimetrically as above.

3. Four samples (*C*1 to *C*4) were treated exactly as the *A* samples, except that "pure" toluene, once distilled, was used.

4. Four samples (*D*1 to *D*4) were treated as the *A* samples, except that "pure" toluene as supplied was used.

Results.

The results are summarized in Table II. Those results obtained by the colorimetric method are only approximate, since sample *A*1 was taken as the standard and all other colorimetric values are relative to *A*1. At this time no pure pregnanediol was available for preparation of an absolute standard. Comparisons were made in a "Klett" visual colorimeter.

The obvious feature of the results is that the same weight of pregnanediol, within limits of accuracy satisfactory for clinical use, was obtained by using all the modifications considered, except when only a single precipitation was applied (*A*4, *C*4 and *D*4). From this

experiment the following conclusions were drawn in regard to the proposed modifications of Marrian's method.

Firstly, the centrifuging time may be reduced in most cases to thirty minutes.

Secondly, "pure" grade or once-distilled toluene may be used for both gravimetric and Goldzieher methods.

Thirdly, Goldzieher colorimetric estimation gives results of reasonable accuracy at the second or third precipitation stages, but not at the first. Hence, in view of the unpleasantness of working with acetyl chloride, and of the time necessary to apply this colour test, it seemed preferable to weigh the product rather than to use this colorimetric modification.

Fourthly, gravimetric results obtained after only two precipitations agreed reasonably well with those found with the prescribed triple precipitation. It is obvious that the high values obtained with a single precipitation are due, at least in part, to failure to remove completely sodium hydroxide added to effect the precipitation of the pregnanediol. It might be thought that only two precipitations would be insufficient to remove all the sodium hydroxide; but a simple calculation will show that, if as much as 0·5 millilitre of liquid remains each time after centrifugation and removal of the supernatant fluid, then only 0·05 milligramme of sodium hydroxide passes through to the final precipitate to be weighed as pregnanediol. This amount is obviously negligible.[1]

TABLE II.

Sample.	Milligrammes of Pregnanediol per 250 Millilitres of Urine.	
	Gravimetric Method.	Colorimetric Method.
*A*1	5·7	5·7
*A*2	4·7	5·3
*A*3	7·3	6·0
*A*4	15·3	11·4
*B*1	4·6	—
*B*2	4·6	—
*C*1	4·7	5·1
*C*2	6·6	5·7
*C*3	5·5	6·2
*C*4	12·9	11·4
*D*1	4·7	4·6
*D*2	5·1	5·0
*D*3	5·9	6·6
*D*4	17·6	14·0

VERIFICATION OF CONCLUSIONS.

In order to verify these conclusions, and at the same time to compare Guterman's and Goldzieher's colorimetric tests, a further experiment in slightly modified form was devised.

Twelve 250 millilitre samples from a pooled specimen of urine from pregnant women were treated as follows.

1. Four samples were extracted with purified toluene. Duplicates *A*1 and *A*2 were subjected to the complete Marrian method, and the products were estimated gravimetrically. These two served as standards. Later pregnanediol in *A*1 was estimated by Goldzieher's colour reaction, while *A*2 was treated with concentrated sulphuric acid according to Guterman's colorimetric estimation. *A*3 and *A*4 were duplicates treated as above, except that the products were estimated gravimetrically after only two precipitations; Goldzieher's reaction was applied to *A*3, while *A*4 was estimated colorimetrically by Guterman's reaction.

2. Duplicates *B*1 and *B*2 were extracted with purified toluene and precipitated three times, but spinning time after each precipitation was reduced to thirty minutes. After being weighed, *B*1 was subjected to Goldzieher colorimetric estimation, while *B*2 was treated according to Guterman's techniques.

3. Four samples (*C*1 to *C*4) were treated exactly as *A*, except that once-distilled toluene was used.

4. Duplicates *D*1 and *D*2 were subjected to all the above modifications, in order to see whether a summation of the slight errors introduced by each modification might cause too great a deviation in the final result. Hence *D*1 and *D*2 were extracted with once-distilled toluene, precipitated only twice, and centrifuged for thirty minutes after each precipitation. The products were weighed, and later *D*1 was subjected to Goldzieher colour development, while *D*2 was treated according to Guterman's method.

The results of this experiment are summarized in Table III. The colorimetric values are, as before, only approximate, since it was necessary to use *A*1 as the standard for Goldzieher colorimetric comparisons, it being assumed that the colour developed with sample *A*1 was equivalent to 2·7 milligrammes of pregnanediol, and all other Goldzieher estimations being made relative to this. Similarly, *A*2 was taken as the standard for Guterman colorimetric estimations.

TABLE III.

Sample.	Milligrammes of Pregnanediol per 250 Millilitres Volume.		
	Gravimetric Method.	Goldzieher Method.	Guterman Method.
*A*1	2·7	2·7	—
*A*2	2·8	—	2·8
*A*3	3·0	3·2	—
*A*4	2·9	—	3·9
*B*1	3·0	2·4	—
*B*2	3·0	—	5·0
*C*1	2·8	2·2	—
*C*2	2·5	—	4·5
*C*3	2·4	3·0	—
*C*4	2·9	—	5·3
*D*1	3·1	2·4	—
*D*2	2·8	—	5·6

These results confirmed previous observations, and showed that the combination of all modifications (*D*) did not appreciably affect the results when gravimetric estimation was used. The last-mentioned method appeared to give the most reliable results. The Goldzieher colorimetric estimations approximated fairly closely to the gravimetric values, but Guterman' colour development appeared to give somewhat higher values.

As a result of these experiments it was decided to introduce as a routine the following procedures: (i) the use of once-distilled toluene (fraction boiling at 110° C.); (ii) precipitation of the pregnanediol only twice; (iii) thirty minutes' centrifugation only, after each precipitation; (iv) final gravimetric estimation.

At this stage other slight adjustments were also introduced for convenience—namely, the volume of aliquots assayed, the number of toluene extractions and the volumes of sodium hydroxide and water used to wash the pregnanediol extracts.

Instead of making a twenty-four hour specimen up to 2·5 litres and using 500 millilitre aliquots, it was found more convenient to measure the volume of the twenty-four hour specimen and use aliquots of one-fifth, one-sixth or one-seventh of the total volume, such that a volume between 250 and 300 millilitres was processed. This volume was convenient for 500 millilitre "Quickfit" flasks. The volume of concentrated hydrochloric acid added to effect hydrolysis now required adjusting; the amount of 10 millilitres per 100 millilitres of urine to be hydrolysed, advocated by both Guterman and Marrian, was adopted.

Since Guterman (1948) claims to achieve quantitative results with only one toluene extraction, it was decided to eliminate one of the toluene extractions, but to safeguard accuracy by continuing to make two extractions and by quantitative transferences of toluene extracts wherever

[1] The amount of sodium hydroxide remaining after two precipitations is calculated as follows. At the first precipitation, pregnanediol is precipitated with 16 millilitres of decinormal sodium hydroxide solution. One millilitre of decinormal sodium hydroxide solution contains four milligrammes of sodium hydroxide. The mixture is spun and the supernatant fluid is removed. If 0·5 millilitre of supernatant remains, this contains approximately two milligrammes of sodium hydroxide. At the second precipitation, the sodium hydroxide is diluted with 20 millilitres of alcohol and water. One millilitre of supernatant then contains 2/20 = 0·1 milligramme. If 0·5 millilitre is not removed, then 0·05 milligramme of sodium hydroxide passes through to the final precipitate and is weighed as pregnanediol.

necessary. This resulted in some saving of time and economy in toluene, both of which are desirable.

Since only 150 millilitres instead of 200 millilitres of toluene were now being used in each estimation, the toluene extract after filtration on a Buchner funnel amounted to about 165 millilitres, including toluene washings added in quantitative transferences. Guterman and Marrian used 30 millilitres of normal sodium hydroxide solution or water per 100 millilitres of toluene, so two 50 millilitre washes with normal sodium hydroxide solution followed by two 50 millilitre washes with distilled water were introduced.

Modified Marrian Method.

The method in use in this laboratory at the present time may now be stated as follows.

A twenty-four hour specimen of urine is collected in a vessel containing a few drops of o-cresol as preservative. The volume is measured, and convenient duplicate aliquots of 250 to 300 millilitres (usually one-fifth or one-sixth of the total volume) are measured into 500 millilitre Florence flasks with "Quickfit" necks.

Hydrolysis and Extraction.

To the urine in the flasks are added 100 millilitres of toluene (once distilled, boiling point 110° C.) and a few washed pebbles to prevent bumping. The mixture is brought to boiling point under reflux over a hot plate, concentrated hydrochloric acid (10 millilitres per 100 millilitres of urine) is then poured down the condenser, and boiling is continued vigorously for ten minutes.

The flask is cooled rapidly under the tap, and the contents are transferred to a separating funnel and shaken vigorously. After five to ten minutes' settling, the urine layer is run back into the Florence flask, and the toluene and emulsion layers are collected in a 250 millilitre Erlenmeyer flask. The urine layer is extracted once more by vigorous shaking in the separating funnel with 50 millilitres of toluene. The urine layer is discarded and the toluene and emulsion layers are added to that obtained by the first extraction.

The combined toluene extract is filtered through a Whatman number 1 filter paper on a Buchner funnel with gentle suction, and the filtrate is transferred to a clean separating funnel. After the small layer of urine which collects has been run off, the toluene extract is washed by vigorous shaking with two 50 millilitre volumes of normal sodium hydroxide solution, and then with two 50 millilitre volumes of distilled water.

The washed toluene extract is evaporated to dryness *in vacuo*. Every transference of toluene extracts in the procedure described above is carried out quantitatively by the use of small rinsings of toluene when necessary.

Precipitation and Estimation of Pregnanediol.

The residue is dissolved in four five-millilitre volumes of absolute alcohol, and transferred quantitatively to a 50 millilitre centrifuge tube by means of a Pasteur pipette. The alcohol is evaporated off in a boiling water bath over a hot plate.

Exactly four millilitres of absolute alcohol are then added, and the tube is placed in a water bath maintained at 75° C. Exactly 16 millilitres of decinormal sodium hydroxide solution are added dropwise from a burette during three minutes, the mixture being constantly stirred with a glass rod. The water bath containing the tube is transferred to an incubator at 37° C. and left overnight.

Next morning a small quantity of "Hyflo Supercel" is well mixed with the material in the centrifuge tube, which is then spun for thirty minutes at 3500 revolutions per minute. The supernatant fluid is removed by means of a Pasteur pipette, and the residue reprecipitated under the same conditions as above; however, 16 millilitres of distilled water are used instead of decinormal sodium hydroxide solution. The mixture is incubated at 37° C. for only two hours in this reprecipitation, and centrifuged for thirty minutes without the addition of more "Supercel".

After removal of the supernatant fluid, five millilitres of absolute alcohol are added to the residue and the tube is placed in a water bath at 75° C. for one minute. A small quantity (approximately 10 milligrammes) of animal charcoal is added and the mixture is stirred with a glass rod, the water bath being kept at 75° C. At the end of two minutes this mixture is filtered through a fluted filter paper (Whatman number 1) into a weighed glass tube. Two millilitres of absolute alcohol are added to the centrifuge tube, then passed through the filter paper, and the washing with two millilitres of alcohol is repeated twice more.

The tube containing the filtrate is transferred by means of tongs to a boiling distilled water bath. (These precautions are necessary to ensure constant weight of the weighing tube.) After evaporation to dryness, the tube is taken from the water bath with tongs, wiped with a clean dry towel, placed in a vacuum desiccator for two hours, and then weighed. A further period of two hours in the desiccator ensures constant weight.

The amount of pregnanediol excreted per twenty-four hours is then calculated.

Comparison of Marrian's Short Method with the Modified Method.

A reliable method of estimating pregnanediol in routine clinical practice was now in operation, the main disadvantage of the method still being its lengthiness. Consequently the publication of Marrian's short method was of great interest, and a comparison with the modified procedure was made.

Twenty-four hour specimens of urine were collected from 20 pregnant women, and the pregnanediol was estimated by the following methods, each carried out in duplicate.

Scheme.

Marrian's modified method was carried out in duplicate assays on 20 cases, the following being used: (i) final gravimetric estimation of pregnanediol, and (ii) final colorimetric estimation of pregnanediol on eight of these cases. At the same time, Marrian's short method (see below) was carried out in duplicate assays on the same 20 cases, the following being used: (iii) final gravimetric estimation of pregnanediol, and (iv) final colorimetric estimation on the same eight cases as in (ii). Method (i) was considered to be the standard, with which the results of the other methods were compared.

Method.

The method used to estimate the pregnanediol in the specimens from the 20 cases referred to in (i) above has been previously described under the heading "modified Marrian method".

In order to make the eight colorimetric estimations in (ii) above, residues of eight of the 20 samples made according to (i) were treated as follows.

After the addition of 10 millilitres of concentrated sulphuric acid to the residue in the tube, it was placed in a water bath at 25° C. for twenty minutes and occasionally stirred with a glass rod. The colour developed was then estimated in a photoelectric colorimeter, a blue-violet filter being used. By comparison with a calibration curve made with known amounts of pure pregnanediol (0·5, 0·75, 1·0, 1·25 millilitres of a 0·1086% solution), the amount of pregnanediol was determined. If the colour developed in the unknown solution was so deep as to fall outside this range, the solution was suitably diluted with concentrated sulphuric acid.

Marrian's short method was used to estimate pregnanediol in 20 samples from the same patients as in (i) by the following procedure.

Hydrolysis and Extraction.—Duplicates of 100 millilitres of urine from each of the 20 specimens were measured into 500 millilitre "Quickfit" flasks, 50 millilitres of toluene (once distilled, boiling point 110° C.) and a few pebbles were added, and the mixture was brought to boil under reflux. Ten millilitres of concentrated hydrochloric acid were then added and the boiling was continued for ten minutes. The flask was cooled rapidly under the tap, and the contents were poured into a separating funnel and shaken well. After five to ten minutes' separation, the urine layer was reextracted with 15 millilitres of toluene and then discarded. The toluene and emulsion layers were filtered through a Whatman number 1 filter paper on a Buchner funnel. The filtrate was washed in a separating funnel twice with 15 millilitres of normal sodium hydroxide solution, and then twice with 15 millilitres of distilled water. The washed toluene extract was evaporated to dryness *in vacuo*. Care was taken that every transference was quantitative.

Precipitation and Estimation of the Pregnanediol.—The residue was dissolved in absolute alcohol and quantitatively

TABLE IV

Comparison of Results Obtained by the Modified Marrian Method and the Short Marrian Method, by Both Gravimetric and Colorimetric Techniques.

Test Number.	Gravimetric Method.			Colorimetric Method.		
	Milligrammes of Pregnanediol in Twenty-four Hours.		Percentage Error in Short Method.	Milligrammes of Pregnanediol in Twenty-four Hours.		Percentage Error in Short Method.
	Long Method.	Short Method.		Long Method.	Short Method.	
1	34·5	63·8	85			
2	7·0	21·6	200			
3	20·0	22·0	10			
4	5·5	8·0	42			
5	26·5	46·7	76	30·5	42·2	59
6	77·0	64·0	−17			
7	85·4	95·5	12			
8	24·2	36·5	50			
9	78·0	85·0	9			
10	16·2	35·0	120			
11	12·0	23·5	50			
12	7·8	31·9	310			
13	16·1	31·8	50			
14	26·3	26·5	0	25·1	24·7	−6
15	51·0	48·9	−4	57·3	39·2	−24
16	14·4	19·8	37	12·7	17·8	24
17	8·8	24·0	173	9·8	16·9	100
18	22·8	49·7	118	23·9	34·3	50
19	11·3	28·9	156	10·8	27·7	145
20	35·4	58·8	66	33·7	50·7	43

transferred to a one-inch test tube with a mark at the five millilitre level, about 20 millilitres of absolute alcohol in all being used. The alcohol was evaporated to the five millilitre level in a boiling water bath, then the tube was placed in a water bath at 75° C. and stirred with a glass rod while 20 millilitres of decinormal sodium hydroxide solution were added dropwise from a burette over a period of three minutes. The tube in its water bath was placed in an incubator at 37° C. for two hours. The mixture was then filtered with gentle suction through a sintered glass filter of medium porosity, and the pregnanediol precipitate was washed four times with five-millilitre volumes of distilled water (or until the washings were neutral to litmus) to remove all traces of sodium hydroxide. The filter flask was changed, and the pregnanediol was washed through into a one-inch filter tube by means of three five-millilitre volumes of boiling alcohol, assisted by gentle suction. The volume of the filtrate was reduced by evaporation on a boiling water bath to approximately five millilitres, and the tube was then placed in a water bath at 75° C. A few milligrammes of "Norite" (Carbo Union) were added, and after two minutes' stirring the contents of the tube were filtered through a fluted Whatman number 1 filter paper into a weighed glass tube. After three rinsings with two millilitres of alcohol, as described under "modified Marrian method", the contents of the weighed tube were evaporated to dryness, and the tube was dried for two hours in a vacuum desiccator and weighed.

The amount of pregnanediol excreted in twenty-four hours was calculated from the amount found in the volume tested.

Colorimetric Estimations.

Guterman's colorimetric estimation was applied to the final residues obtained by the short method from eight samples, exactly as described in (ii) above.

The pregnanediol solution used for these colorimetric estimations was prepared from a sample of sodium pregnanediol glycuronidate obtained from Ayerst, McKenna and Harrison, Proprietary, Limited (Canada).

Sodium pregnanediol glycuronidate, 0·1968 gramme, was refluxed with 200 millilitres of distilled water and 200 millilitres of purified toluene. Twenty millilitres of concentrated hydrochloric acid were added, and boiling was continued vigorously for fifteen minutes.

After rapid cooling under the tap, the mixture was transferred to a separating funnel and shaken vigorously. The toluene extract was collected, and the aqueous layer was reextracted twice more with 100 millilitre volumes of purified toluene. The combined toluene extracts were evaporated *in vacuo* and the residue was transferred quantitatively to a weighed tube by means of small volumes of absolute alcohol. The alcohol was removed by evaporation in a distilled water bath, and after drying over calcium chloride *in vacuo*, the tube was weighed.

By this procedure 0·1086 gramme of pregnanediol was obtained, which represents a yield of 92·5%. This pregnanediol was dissolved in absolute alcohol to give a standard solution containing 1·086 milligramme of pregnanediol per millilitre. This solution was used in making comparisons by the photoelectric colorimeter.

As a matter of interest, pregnanediol of sufficient purity for colorimetric standards has also been prepared from the following sources: (i) pregnanediol obtained by treating 30 litres of urine from pregnant women (see method described below); (ii) pregnanediol collected from routine estimations carried out by the original complete Marrian method; (iii) pregnanediol collected from routine estimations carried out by the modified Marrian method.

The methods are as follows.

1. Thirty litres of urine from pregnant women were treated in volumes of approximately 1500 millilitres by a combination of Venning's and Marrian's methods. After triple extraction with a total of 1500 millilitres of butanol, the extract was evaporated to dryness *in vacuo*, the residue hydrolysed and extracted with toluene. After evaporation of the toluene, the residue was solved in 20 millilitres of absolute alcohol and the pregnanediol was precipitated with sodium hydroxide at 75° C. The precipitate was collected by centrifuging, washed with water and centrifuged again. The crude pregnanediol was then transferred to a stoppered weighing bottle by means of alcohol.

When the pregnanediol from thirty litres of urine had been collected in this way, it was purified by three crystallizations from absolute alcohol. A white crystalline solid resulted, melting point 227° to 232° C. (corrected).

2. The pregnanediol collected from routine tests performed by Marrian's complete method with purified toluene was subjected to two recrystallizations from absolute alcohol, and when it was examined microscopically in an alcoholic medium, needle-shaped crystals in feathery or star-like arrangement were observed. Dry crystals examined microscopically appeared as elongated hexagons in criss-cross and rosette formation. The final preparation was too small to test its melting point.

3. Pregnanediol collected from routine tests performed by the modified Marrian method was purified by two recrystallizations. There resulted white flaky crystals, melting point 231° to 233° C., which appeared under the microscope as large hexagonal crystals, smaller less perfect hexagons and knife blades.

Results.

The results of these investigations are set out in Table IV, and in every case are the average of duplicate tests. The results obtained by the modified Marrian method are taken as the standard, and percentage errors involved in the use of the short method are calculated on this basis. When the gravimetric procedure was used, the short method gave results up to 310% higher than those obtained by the longer method. In only six instances was the deviation less than 20%. The colorimetric modification reduced the

error somewhat, but even then it was more than 20% in all cases except one.

DISCUSSION.

This investigation shows that variable amounts of impurities, depending on the particular urine being tested, are retained in the shortened procedure, so that gross errors are involved in many assays. If this method was used for the estimation of pregnanediol in urine, the result would almost invariably be too high and the necessary hormonal therapy would not be given.

It was interesting to notice that there was consistent agreement between the results of the long and short methods in tests on several different specimens from one particular patient, Mrs. M. (tests 4, 6, 14 and 15). This probably indicates that certain urine contains only small amounts of the interfering impurities, while other urine contains larger quantities.

CONCLUSION.

These investigations show that the shortened Marrian method cannot be used with any degree of accuracy in the estimation of urinary pregnanediol, whether the gravimetric or colorimetric procedure is employed. The colorimetric form of the modified Marrian method is quite as satisfactory as the gravimetric method, but no time saving is effected by the colorimetric procedure, as calibration curves need to be prepared frequently, and it is found simpler to eliminate the sulphuric acid treatment and continue to weigh the product.

In spite of the fact that a single estimation by the modified Marrian method cannot be completed under two days, one person can commence three estimations per day, and in this way complete fifteen estimations per week. However, the nature of the method is such that it is desirable for the person making pregnanediol estimations to be as undisturbed as possible by other laboratory work.

Thus it has been regretfully concluded that, although the modified Marrian method is more tedious than the shortened procedure, it must continue to be used in this laboratory in view of its greater accuracy.

ACKNOWLEDGEMENTS.

My thanks are due to three members of the department of pathology of the Women's Hospital: first and foremost, Dr. V. I. Krieger for constant help and encouragement; Miss B. Liddelow for permission to include the results of eleven duplicate assays which she made by means of the original Marrian method; and Dr. H. F. Bettinger for constructive criticism of the article. I should also like to thank Mr. Holden, of the Walter and Eliza Hall Institute, for instruction in the use of the photoelectric colorimeter; Professor V. M. Trikojus, of the department of biochemistry, University of Melbourne, for supplying "Supercel" and alumina; Mr. Stevenson, of the department of chemistry, University of Melbourne, for information on purification of toluene and for supplying pure substances for calibration of our thermometer; and Ayerst, McKenna and Harrison, Proprietary, Limited, for supplying one gramme of pure sodium pregnanediol glycuronidate.

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Reviews.

PRINCIPLES OF COLORIMETRY.

PIETER JOHANNES BOUMA died in January, 1947, but in the previous year the results of his many experiments and much thinking in colorimetry had been assembled and published in book form in Dutch. The English translation bearing the title "Physical Aspects of Colour"[1] was carried out in 1947 and was published in 1949.[1] This learned work may be taken as supplementing and to a certain degree supplanting A. C. Hardy's "Handbook of Colorimetry" (Cambridge, Massachusetts, 1936). Much of the treatment is original and a logical sequence is manifest in the presentation. The main aim of the book is to put on a sound basis of theory and practice the measurement of colour by geometrical and numerical means. The relations of colour with art and the æsthetics generally are not discussed; neither is the chemistry of pigments. The physiological and psychological aspects are examined only as far as is necessary for a better understanding of the physical aspect. An atmosphere can be described as chill, raw, searching, relaxing or hot, but these terms are related to human sensation only; scientific description limits itself to numerical estimates of temperature, humidity and wind velocity. In the same way colours may be named by household or trade terms—cobalt blue, rose pink, apple green and the like, but matching cannot take place unless a permanent sample of each is kept for comparison. Is it possible to express colours by exact magnitudes of proper coordinates? It is, but the task is beset by physiological and psychological difficulties. There are three qualities in any coloured body which must be taken into account: hue, saturation and brightness. Now hue and saturation can be expressed numerically by the colour triangle in which the straight base represents the purples in between red and violet, whilst the two sides somewhat convex outwardly, and subtending a blunt apical angle, denote the curtailed octave from red to violet. Near the centre of the triangle is a point connoting white. Any point on the bounding lines other than the base represents a pure spectral colour; a line joining this with the white point and produced to the opposite side gives the complementary colour. A point within the area of the triangle, not the white point, indicates a colour with a certain admixture of white, in other words a departure from saturation. This colour triangle is, of course an old device, but in this book there are geometrical complexities elaborately analysed and presented to meet all the intricacies of modern colour shades. It would be a mistake to regard this colour triangle as an application of pure physics, for it is based on the inability of the eye to analyse wavelengths in the same way as the ear does tones, with the result that a mixture of two spectral colours sent into the eye gives the sensation of a colour the wave-lengths of which are not present. Brightness requires separate treatment and is studied under the headings physical brightness, apparent brightness and subjective brightness. Many examples are given of the ability to represent by coordinates

[1] "Physical Aspects of Colour: An Introduction to the Scientific Study of Colour Stimuli and Colour Sensations", by Dr. P. J. Bouma; 1949. Eindhoven, Holland: N.V. Philips Gloeilampenfabrieken. Sydney: Philips Electrical Industries of Australia Proprietary, Limited. 9" × 6¼", pp. 316, with 113 illustrations. Price: £1 17s. 6d.

colours of every possible hue and degree of saturation. The practical applications of colorimetry are manifold. Artificial illumination should vary as it is designed for street, office, dining room ("potatoes and butter must not look green"), factory and shop. The theory underlying the defining of colours is also of immense importance with dyes, enamels, paper, textiles, flowers, colour printing, colour photography, colour film projection and colour television. The subject is handled with considerable physiological and geometrical complexity, but fortunately no demands are made on the reader's mathematical knowledge beyond high school standards. The medical man can read with profit the chapter on colour blindness.

A few matters demand special commendation. Bouma assumes that the eyeball is not rigidly fixed when the visual axis is directed towards any object, but that some oscillation is present; this means that the image of a small object, such as a star, moves on the retina and passes from cone to cone in the fovea. This consideration, we might add, renders almost worthless the two-point discrimination method of determining visual acuity. Professor Hartridge meets this criticism by denying that the eyeball has any tremor, a contention contrary to physiological principles. The contribution of Goethe to colour lore is discussed with sanity and restraint, the author being unlike certain German psychologists who hold up the poet as a scientific panergon. Minor criticisms are the following. More should have been made of the researches of Clerk Maxwell, though what is given is appreciatory. In the matching of a white or coloured field with a standard in photometer or colorimeter the warning of J. S. Haldane is frequently forgotten that what is physically fixed and constant is, owing to retinal fatigue, shifting in sensational value. Haldane in his hæmoglobinometer got over this difficulty by alternating the "fixed" and variable fields. Bouma makes no mention of this important consideration. On page 270 is the following: "According to the classical theory of Descartes (1637) the rainbow colours are indeed practically pure spectral colours determined by the dispersion of drops of water in which sunlight is refracted." Descartes gave the world the geometrical principles underlying the circular form of the bow, but he failed to explain the colours—that was reserved for Newton. There is a useful list of symbols employed; also a geod working bibliography except perhaps as regards the many new hypotheses of colour vision. The index might with advantage be extended.

BRAIN AND BEHAVIOUR.

IN "Brain and Behaviour" N. E. Ischlondsky describes induction as a fundamental mechanism of neuropsychic activity.[1] He gives credit to E. Hering for originating the concept of induction in 1878. He discovered a halo around an after image and conceived a process of increased nervous excitability emanating from an adjacent focus of inhibition. In 1906 Sherrington discovered relationships similar to the above in the spinal cord. Muscle activity of one group of muscles is accompanied by inhibition of another. Later Pavlov and his co-workers considered the differentiation of conditioned responses and discovered the induction of increased excitability through the preceding use of inhibition.

The author proceeds to reinvestigate the above theses and gives diagrams in colour to demonstrate the principles of induction. It is apparent that the concept has engaged his attention for many years.

Finally he proceeds to correlate his experimental findings with clinical and sociological material.

Following the example of Freud, he analyses the oddities of ordinary behaviour, commencing with the ambivalency of tears and laughter. Children cry for no adequate reason. Tiredness represents widespread inhibition which provokes by induction the opposite of excitation and the child cries.

Dr. Ischlondsky points out our tendency to blurt out words exactly opposite to those intended.

He gives instances of people whose lives were profoundly influenced by a rebound of emotion. Thus, a young woman twice jilted by young men, happily marries a man forty years her senior. Another hurls herself into a vivid life of blatant homosexuality. In sexuality he notes the effect of contrasts. Men and women choose mates who are so different as to be objectively unsuited.

The author is at variance with Freud on the mechanism of sublimation. He accuses the Freudian concept as being mechanical. Sublimation is possible only when the brain cortex has been made receptive and is a propitious ground for induction. Thus whilst a scientist can sublimate his sexual urges into the scheme of scientific activity, a similar attempt by an untrained labourer would result in failure and a heightened sexuality.

In applying induction to sociology, the author points out that induction is a natural process which is essential to harmonious living. It can be controlled only by training and self-discipline throughout life. There must be consistency of effort, otherwise the swing to the opposite gets out of hand. He pleads for our legislation to give us consistent laws and a planned discipline in order to create true moral values.

"Brain and Behaviour" is a stimulating work which at times defeats its objective. The author may be accused of special pleading, but it is seldom that a writer with a new message can be entirely free from this error. Surely it may be described as a side effect of the inductive process. This book is well worth a perusal by those who are interested in the mechanisms of the mind.

[1] "Brain and Behaviour: Induction as a Fundamental Mechanism of Neuro-Psychic Activity. An Experimental and Clinical Study with Consideration of Educational, Mental-Hygienic and General Sociological Implications", by N. E. Ischlondsky, M.D.. London: Henry Kimpton. 9¾" × 6", pp. 204, with 46 illustrations. Price: 21s.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Notes on M & B Medical Products", Fifth Edition; 1950. Dagenham and England: May and Baker, Limited. 7" × 5", pp. 190.

Information on new and established "M & B" preparations.

"Synopsis of Endocrinology", by Ross Wilson Hawker, M.B., B.S. (Sydney); 1950. Brisbane: William Brooks and Company (Queensland) Proprietary, Limited. 8½" × 5½", pp. 230.

Aims to present to the student of medicine a brief survey of the endocrine system.

"The Surgical Clinics of North America" (issued every two months), February, 1950. Chicago Number. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9" × 6", pp. 318, with 82 illustrations. Price: £6 (paper binding) and £7 (cloth binding) per clinic year.

Contains a symposium on urology, and a symposium on gynæcology and obstetrics, each dealing with conditions which occur most frequently in everyday practice.

"Major Symptoms in Clinical Medicine", by John Almeyda, M.R.C.P., D.P.H. (London), M.R.C.S. (England), with a foreword by Sir Adolphe Abrahams, O.B.E., M.A., M.D. (Cambridge), F.R.C.P. (London); 1950. London: Henry Kimpton. 9½" × 6¼", pp. 392, with 185 illustrations. Price: 25s.

Deals with symptoms, their anatomical and physiological aspects, mechanism, significance and mode of investigation.

"The Asthmatic Child: The Prevention of Asthma by Simple Home Methods", by G. F. Walker, M.D., F.R.F.P.S.G., D.C.H., M.R.C.P.; 1950. Bristol: John Wright and Sons, Limited. London: Simpkin Marshall, Limited. 8½" × 5½", pp. 19, with many illustrations. Price: 2s. 6d.

A book for the guidance of parents of asthmatic children.

"A New Approach to the Treatment of Burns and Scalds", by Leonard Colebrook, F.R.S., F.R.C.O.G.; 1950. London: Fine Technical Publications. 8½" × 6", pp. 174, with illustrations. Price: 12s. 6d.

A discussion of the treatment of burns, based on wide experience, with control over infection as its central point.

"A Short History of Sex-Worship", by H. Cutner; 1950. London: C. A. Watts and Company, Limited. 7½" × 5", pp. 222. Price: 2s. 6d. (paper binding) and 5s. (cloth binding).

A historical account of "one of the strangest of all superstitions".

The Medical Journal of Australia

SATURDAY, JUNE 24, 1950.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

A NEW MEDICAL BILL IN GREAT BRITAIN.

THE recent introduction into the British Parliament of a Bill for "an Act to amend the *Medical Acts* and for purposes connected therewith" is of particular interest to Australians. Reference to THE MEDICAL JOURNAL OF AUSTRALIA of April 13, 1940, will show that before that date several of the Australian States had proposed to make it compulsory for students in medicine after graduation to serve for a period as hospital resident medical officers before they could be registered. In our discussion on that occasion the provisions of *The Medical Act of 1939*, of Queensland, were reproduced in full, and it was pointed out that they might possibly affect reciprocity between the Australian States and Great Britain. On account of the war, consideration by the General Medical Council of Great Britain was deferred, but not before Sir Norman Walker, the president, had had a good deal to say on the matter.[1] With a certain amount of righteous indignation he stated his opinion that the General Medical Council should have been consulted before such important changes were introduced.

Since 1940 the ideas, which had been expressed in legal enactments in Victoria and New South Wales and also in Queensland, have been discussed in Great Britain, and the discussions have borne fruit in the new British Bill. Before the new Bill is described it will be well to point out that in 1942 the Medical Planning Commission of the British Medical Association expressed the opinion that it would be to the advantage of everyone concerned if a medical student on graduation could spend some time in practice under supervision before he set up in practice on his own account. This opinion was endorsed by the General Medical Council in 1943. Subsequently the Inter-Departmental Committee on Medical Schools (known as the Goodenough Committee) considered it, and its report stated that in its opinion every student, after he had passed his final qualifying examination and before he was admitted to the Medical Register and allowed to enter independent medical practice, should be required to serve as a junior house-officer for a period of twelve months in one or more approved hospitals. In the new British Bill care is taken that full registration in the medical register shall not be granted without proof of experience. A person claiming registration by virtue of a "qualifying diploma other than a Commonwealth or foreign diploma" must have a certificate of experience according to the provisions of Section 2. If a person claims registration by virtue of a Commonwealth or foreign diploma, the Council has to be satisfied that he has had the requisite experience. Section 2 states that the certificate required "shall not be granted in respect of any person unless after passing a qualifying examination he has been engaged in employment in a resident medical capacity in one or more approved hospitals or approved institutions for such period, not being less than twelve months, as may be prescribed by regulations of the Council approved by order of the Privy Council". The certificate is to be given by the body granting the qualifying diploma, in virtue of which application for registration is made, if that body is satisfied that the regulations regarding resident medical service have been met and if it thinks that the service has been satisfactory. A special section deals with applicants who are the holders of Commonwealth or foreign diplomas, and special attention should be paid to this by graduates of Australian universities. The matters in regard to which the Council must be satisfied before it grants registration, are set out as follows:

> (*a*) that the person claiming registration has been employed as mentioned in subsection (1) of the last foregoing section and has satisfied the conditions specified in paragraphs (*a*) and (*b*) of subsection (2) thereof; or
>
> (*b*) that the said person has rendered satisfactory service in an appointment or appointments (whether within or outside His Majesty's dominions) such as in the opinion of the Council confer experience of the practice of medicine and surgery, or medicine, surgery and midwifery, not less extensive than that required for a certificate under the last foregoing section; or
>
> (*c*) that the said person has otherwise acquired such experience as aforesaid.

After graduation and before he obtains the certificate necessary for full registration, the student shall, on payment of a fee, be admitted to provisional registration. Persons receiving provisional registration shall be registered in a special part of the Medical Register and when they receive full registration their names are to be removed from that part of the register. The functions of provisionally registered persons are set out and the Council is empowered to publish a provisional register from time to time.

Important alterations are to be made in regard to disciplinary provisions. Though the details need not concern us, it should be noted that the disciplinary functions of the Council are to be transferred to, and exercised by, a committee to be known as the Medical Disciplinary Committee. It will consist of the president and eighteen other members, of whom at least six shall be elected members of the Council and at least one shall not hold a medical qualification. Provision is made for appeal to His Majesty in Council by a person who has been condemned to have his name erased from the medical register.

Of special interest is a section of the Bill which provides that the Council may appoint persons, who are not members of the Council, "to visit places where instruction is given to medical students under the direction of any body

[1] *The Lancet*, May 27 and December 3, 1939, pages 1229 and 1184.

having power to grant a qualifying diploma, not being a Commonwealth or foreign diploma". The visitors shall have the duty of reporting to the Council on the "sufficiency" of the instruction given in the places which they visit, and in regard to "any other matters relating to such instruction which may be specified by the Council". The visitors will not be allowed to interfere with the giving of any instruction. On receiving a report from a visitor, the Council will send a copy of the report to the body in question, which may, within a specified time, send to the Council any observations on the report or objections to it. As soon as possible after the expiry of the specified time, the Council will send to the Privy Council a copy of the report and of the reply from the body concerned. This provision gives a great deal of power to the General Medical Council; we should not imagine that it would often have to be used. The fact that the Council has inquisitorial powers may possibly be a stimulant to those inclined to slackness. In Australia there is, of course, no single council with powers covering all the States, which could act as inquisitor or policeman to probe the efficiency and ultimate value of the teaching given in Australian medical schools. Some would doubt whether such a body in this country would find much to do, or having found defects would be able to do much in the way of even suggesting a remedy. Others, maybe, would suggest different ways for the detection of deficiencies. That the authorities in the Old Country see fit to give far-reaching powers to the General Medical Council must be looked on as a sign that, however widely the gateway to medicine may be opened, the standard within those gates shall not be allowed to deteriorate.

Returning to the chief provision of the new Bill—that dealing with the resident medical officer's year between provisional and full registration, we may expect that an effort will be made to give effect to such a provision in Australia. So far the resident year, as we may call it, has not been enforced. Everyone will agree that the requirement is in the best interests of the graduates and the community. One will naturally ask what will happen if the graduates outnumber the available resident positions. Further, the graduate will want to know whether a position will be found for him by the hospital which has given him his undergraduate training, or whether he will have to find one for himself. Whatever happens, careful planning will be necessary, first of all, to provide cover for all graduates, and in the second place to see that the student-graduates are wisely and fairly treated. The exploitation of resident medical officers by hospital authorities has to be remembered as a possibility. In this matter the mere existence of a central inquisitorial and checking authority might be useful.

Current Comment.

PLASTIC MATERIALS IN MEDICINE.

A VAST and ever-increasing array of objects, useful and otherwise, is being produced from plastic materials, and we are already rather *blasé* about this intriguing development of modern science. In the fields of medicine and surgery, many familiar articles are being made from plastic materials with advantage, though they excite little comment. Certain specialized developments, on the other hand, are of great interest. Brief reference to some of them has been made by John T. Scales,[1] of the Plastics Research Unit of the Institute of Orthopædics (University of London), Stanmore, Middlesex. As a development from the investigation of the use of polyester resins for the manufacture of orthopædic appliances, these synthetic materials have been applied in other ways. They are produced in industry, Scales explains, for a number of purposes, such as the manufacture of paint, electrical insulation, the hulls of boats and aircraft components. Their chemical structure and production, which Scales outlines, need not concern us here, but they have proved superior to other materials in, for example, the preparation of internal casts of joints and organs. The appropriate resin, in liquid state, may be introduced into such a complex joint as the knee-joint by means of multiple injections, and by movement of the joint be made to flow into all the reflections of the synovial membrane; or it may be run into the trachea and pulmonary vessels (a different colour for each) or into the renal vessels, remaining as a cast of these structures when acid has dissolved away the lung or kidney tissue. Striking colour photographs accompany Scales's paper to illustrate this use of polyester resins. Another useful idea which has been developed satisfactorily is the embedding of museum specimens in transparent resins; this is an improvement on even the best types of jar and makes the specimen easy to handle and display and able to be viewed conveniently from all aspects. Bones can be reproduced in resin, a mould first being made from suitable material and then castings as required; the method, Scales states, is simple and requires little apparatus. The making of orthopædic appliances presents many possibilities, the extent of which is being gradually explored. Scales describes the construction of orthopædic splints and shows an illustration of a polyester resin prosthesis for use after Chopart's amputation; the appliances are light in weight, strong and rigid, and Scales states that in America similar resins have been used for the construction of artificial limbs. The possibilities are almost limitless and we shall look with interest for reports of further ingenuity in this field.

THE EFFECTIVENESS OF WASHING-UP METHODS.

MOST people nowadays have heard that infection can be passed on by way of eating utensils and that unsatisfactory washing-up methods are a danger to public health. However, those who from necessity or choice take meals in public eating houses generally fall back on the adage that what the eye (lacking a high-power lens) does not see the heart (being easily bluffed) does not grieve; in any case, they tend to feel that they cannot do anything about it, and if they could would not know how to go about it. Those whose business it is to know how to go about it will be interested in an investigation by Marcella Higgins and Betty C. Hobbs[2] of washing-up techniques employed in the kitchens of some 30 different establishments serving meals to the British public. They included school and factory canteens, cafés, public houses and more exclusive restaurants. Visits were made during the luncheon rush-hour when conditions were judged to be at their worst. The investigation was particularly concerned with the number and type of bacteria remaining on the various utensils after washing, but included also the degree of bacterial contamination of rinsing water and drying towels. The results illustrate strikingly the variety of factors involved and the way in which one faulty factor can nullify the effect of care and equipment that are otherwise satisfactory. As Higgins and Hobbs state, bacterio-

[1] *The Lancet*, April 29, 1950.

[2] *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service Directed by the Medical Research Council*, February, 1950.

logical cleanliness can be achieved only by rigid attention to every detail of personal and kitchen hygiene. However thorough may be the preliminary removal of food residues from the utensils by soap or other detergents, the rinse-water rapidly becomes heavily contaminated unless it is sufficiently hot and very frequently changed. If the final rinse is in very hot (not less than 180° F.) clean water, the crockery is practically sterilized and will quickly dry in the air without needing the application of a drying cloth which tends to be a potent agent of infection. Higgins and Hobbs quote laboratory observations showing that bacterial counts of crockery may rise by more than one hundred-fold after the application of a used drying cloth. When the rinse-water has a high bacterial count the drying cloth quickly becomes contaminated; this occurred, as would be expected, at premises with only one sink for washing up, but also, more treacherously, at many premises with a mechanical dish-washing machine in which the rinse-water was allowed to drop below the desirable temperature, the utensils often needing to be hand-dried. The degree of contamination of a towel and the speed with which this is attained are directly proportional to the bacterial content of the rinse-water. The state of towels sampled at random was regarded in this investigation as giving a good indication of the general hygiene of the kitchen. The only washing-up method of those investigated which produced a reasonable proportion of articles with the United States Public Health Service standard of less than 100 organisms per utensil was that in which hot water "sterilization" was used. Hypochlorite is an effective sterilizing agent only so long as the water is relatively free from protein matter, and subsequent rinsing is needed to remove the objectionable taste. Quaternary ammonium compounds are still on trial. In passing it is interesting to note that cracked cups washed and rinsed under the same conditions as whole cups can have bacterial counts of the same order; both cracked and whole cups, with pre-cleaning counts in the hundreds, yielded counts of less than 10 per cup after immersion for two minutes in rinse-water at 180° F. and air-drying. The implication, of course, is not that we may view cracked cups with equanimity, but that we may not view whole cups with complacency unless we are sure that they have had adequate contact with, and only with, soap or other detergent and really hot water. This is a disturbingly simple conclusion for our complicated age, but it appears to fit the facts.

FINGER-PULP INFECTIONS.

THE serious practical effects of finger-pulp infections, which tend to be regarded as minor conditions, were referred to in these columns on April 30, 1949, when we quoted the encouraging results obtained by Harrison, Topley and Lennard-Jones in the management of these infections; important features of their treatment were systemic penicillin therapy and minimal incision over the area of greatest tenderness. Another important point about these infections, brought out by H. Bolton, P. J. Fowler and R. P. Jepson,[1] is their frequency, which is much greater than that of the more serious infections of the palmar space or tendon sheaths. Bolton, Fowler and Jepson state that of all claims made under the *Workmen's Compensation Act* in England approximately 2½% to 5% are for septic hand lesions, and analysis of 1979 patients with hand infections treated by them in 1947 indicates that 22% had pulp-space infections, whereas only two patients had infections of tendon sheaths and five infections of the palmar space. They point out that the usual infecting organism is *Staphylococcus aureus*, and as in no more than half the cases was there a history of injury, support the suggestion that the organism may enter by way of sweat or sebaceous gland. The inflammatory reaction causes cellulitis, and this causes pain which is described as "tight" or "prickling". At this stage the infection may resolve spontaneously, particularly when chemotherapy is used. If resolution does not occur, the formation of an abscess is accompanied by "throbbing" pain. From the point of view of treatment, they divide pulp-space infections into three groups: simple felon, suspected bony felon and established bony felon. Simple felon is pulp-space infection limited to soft tissues; with correct treatment it heals without complication. In suspected bony felon clinical and perhaps operative evidence of osteitis is present, but radiographic confirmation is lacking. In established bony felon definite radiographic evidence of bone infection is present. The conservative measures that are sometimes advocated can, these investigators believe, have little application to the treatment of patients who almost invariably have complained of pain for not less than four days before their first attendance at the clinic. In every case without exception in the series studied, pus was found in the pulp space when it was explored. Accepting that the correct treatment for pulp-space infection is incision, Bolton *et alii* believe that the only question to be determined is which incision is the best. Their study of the pathology of these lesions indicates that a local abscess should be drained through the skin immediately overlying it rather than by means of oblique incisions which traverse uninfected pulp tissue and are quickly narrowed by œdema. Small incisions placed directly over the abscess will not damage the nerves, which are displaced laterally. Precise preliminary localization, general anæsthesia and a bloodless field are important points in technique. A small ellipse of cornified epithelium overlying the abscess is excised, and the often small abscess is found. The cavity is filled with penicillin in lactose powder, and the "saucerized" wound is dressed with "Vaseline" gauze without drainage. Active movements are encouraged at once except when immobilization of the finger is required for infective arthritis or of the arm for lymphangitis. Of 50 unselected patients treated in this way, 39 had simple felon and their average healing time was 11·5 days; five had suspected bony felon and their average healing time was 25 days; six had established bony felon and the average healing time was 35 days. When bone infection was suspected or proved, 100,000 units of penicillin were given intramuscularly twice a day for ten to fourteen days; most of these patients had some limitation of movement of the terminal interphalangeal joint at the time of discharge from the clinic. Only five patients complained of a tender scar during the healing stage, and none developed causalgia.

As a supplement to this report, attention may be drawn to the technique of transilluminating the finger tip suggested by E. P. Samuel.[1] After the finger is cleaned (the translucency of thickened epithelium can be increased by painting with cedar-wood oil), it is transilluminated with a naked auriscope bulb pressed gently on successive parts of the finger. The normal pulp has a homogeneous blood-red appearance, the lunula appearing slightly darker. With early pulp infection, deep red shadows spread across the nail, fading and intensifying with the accompanying throbbing feeling; with pure lymphangitis, the pulsation and variations in shadows are less apparent. With effective treatment, the shadows fade and disappear. If the infection progresses, pus forms and is seen as a dark shadow against the pulsation. Pus in the centre of the pulp space is best seen by observation from the palmar aspect with the lamp placed against the nail. Pus will always be found on incision if its shadow has been seen. With late infection transillumination shows the precise extent and location of the slough, but purulent blisters must first be removed. Subungual pus in a paronychia appears as an irregular shadow at the base of the nail and possibly extending beyond the lunula; here again superficial blisters should first have been excised. Pulp infection accompanying early paronychia is seen as a dark shadow extending into the pulp when little clinical evidence exists to suggest its presence. This is a simple technique that Samuel describes, and is rather obvious when it is pointed out. If the shadows are as readily interpreted as he suggests, it should be most useful in aiding the method of simple direct incision of abscesses, which he supports in common with Bolton, Fowler and Jepson, and with Harrison, Topley and Lennard-Jones.

[1] *The Journal of Bone and Joint Surgery*, November, 1949.

[1] *The Lancet*, April 22, 1950.

Abstracts from Medical Literature.

THERAPEUTICS.

Autohæmotherapy in Herpes Zoster.

D. O. POTH (*Archives of Dermatology and Syphilology*, October, 1949) refers to spectacular relief of pain following autohæmotherapy in *herpes zoster* reported by Jone and Alden. The author has treated 141 *herpes zoster* patients who were suffering from pain. Twenty-seven patients received only one injection, 21 received two injections, 77 received three injections, and 16 received four injections. Severe pain had usually subsided before the second or third injection was given. The youngest patient was aged four years and the oldest eighty-two years.

Streptomycin with a Detergent for Local Application.

E. J. GRACE AND V. BRYSON (*Diseases of the Chest*, December, 1949) have successfully treated tuberculous sinuses by the local application of streptomycin dissolved in a germicidal solution of low surface tension. The solution was prepared by dissolving 1,000,000 units of streptomycin in 100 millilitres of a 1:1000 aqueous solution of "Zephiran Chloride", these chemicals being compatible with one another. The advantages of the method are that no more than a small fraction of the quantity of streptomycin required for intramuscular administration is needed; also that the drug is introduced in high concentration at the seat of infection in such a manner that there is intimate contact between the antibiotic and the pathogen.

Coryza Treated with Antihistamines.

J. W. MIDDLETON AND J. A. RIDER (*Diseases of the Chest*, December, 1949) have treated 63 persons suffering from coryza with antihistamine drugs and 29 with inert drugs of similar appearance. Forty-eight of the former group and thirteen of the latter appeared to derive benefit; six colds were aborted in the former group and one in the latter. It was found that neither the duration of symptoms of a cold nor a history of allergy was any indication of the amount of benefit that might be expected.

Ulcerative Colitis.

R. ERLICH (*The American Journal of Digestive Diseases*, January, 1950) describes the treatment of ulcerative colitis with hog stomach. The theory of this treatment was that an antiproteolytic substance in the normal bowel prevented ulcerative colitis, and that the use of hog stomach might prevent the autolysis of the colonic mucosa due to the absence of this antiproteolytic substance. The dose of whole stomach extract was 100 to 120 grammes daily (three tablespoonfuls four times daily). The author found that the method of administration making the preparation most palatable was to place one heaped tablespoonful of hog stomach (10 grammes) on the tongue and follow it by any desired liquid. Twenty-four cases were studied. There were no dietary restrictions. In 88% of cases the patient recovered. The hog stomach used in these cases was that part remaining after the antianæmic principle was substantially removed. The author concludes that the fractional component of desiccated extract of hog stomach is better tolerated and more potent than whole stomach extract. The results appear to have been remarkably good, and the relapses very few and easily controlled by a brief resumption of the treatment.

Para-Aminobenzoic Acid.

C. J. D. ZARAFONETIS *et alii* (*Archives of Internal Medicine*, January, 1950) describe the use of para-aminobenzoic acid in dermatomyositis and scleroderma. Two patients with dermatomyositis and four with scleroderma were treated. Four of the six patients improved. Sodium or potassium para-aminobenzoate was used; four tablets of 0·5 gramme each were given every two hours for five weeks, and the dose was then reduced to 12 to 14 grammes daily. In each case of dermatomyositis and scleroderma the patient made a great improvement.

Typhoid Fever.

VERNON KNIGHT *et alii* (*Archives of Internal Medicine*, January, 1950) describe the results of antimicrobial therapy in typhoid fever. Polymyxin B, aureomycin and chloramphenicol were studied. Four seriously ill patients treated with polymyxin B in moderate to large doses appeared to derive no benefit. Thirty-four patients with typhoid received aureomycin orally for six to ten days. In 53% of these cases no apparent benefit was observed. A dosage of up to 18 grammes of aureomycin per day was given. In general, as only two out of thirty-four patients died, and no severe complications occurred, it is stated that the patients treated with aureomycin probably benefited by the treatment. Chloramphenicol given by mouth to thirteen typhoid patients produced rapid recovery within seventy-two hours, regardless of the severity of the condition, in contrast with aureomycin, after the administration of which fever often lasted two or three weeks. Chloramphenicol was given by mouth five or six times a day in a total daily dosage of 100 milligrammes per kilogram for two or three days, and then 50 milligrammes per kilogram for seven to ten days.

Lithium Salts.

J. H. TALBOTT (*Archives of Internal Medicine*, January, 1950) discusses the use of lithium salts as a substitute for sodium chloride. He states that in renal disease and certain metabolic disorders a substitute for sodium chloride in the diet had been sought. Ammonium chloride and potassium salts had their disadvantages. Lithium, therefore, was used experimentally by the author, firstly in gout, in which a theoretical advantage had been claimed. The author found no support for these claims. In congestive heart failure, as a substitute for sodium chloride, lithium chloride with a trace of citric acid and potassium iodide was employed. Patients did not object to it, and continued its use for up to nineteen days with no ill effects except gastro-intestinal disturbance. There was no evidence of lithium intoxication in the patients studied; it was suggested that signs of weakness or other untoward signs noted might be due to medication with digitalis or mercurial diuretics at the same time. No evidence was adduced as to the beneficial effects of the use of lithium. In gout, lithium salts after several months' use were abandoned, because there was no evidence of any benefit from their use clinically or biochemically.

"Chloromycetin" in Bacillary Urinary Infections.

G. E. CHITTENDEN *et alii* (*The Journal of Urology*, November, 1949) state that the new synthetic antibiotic, "Chloromycetin", is considerably more active against several Gram-negative organisms than against the Gram-positive and acid-fast organisms tested. It is two to sixteen times as active as streptomycin against Gram-negative organisms. It is very stable in neutral and acid ranges, but unstable in strongly alkaline solutions. It can be administered orally and is best given in sealed capsules. The capsules weigh 0·25 gramme, and one capsule is usually given every six hours, though the dosage may be up to double this. When mixed infections are present, adjuvant therapy, such as with penicillin and sulphonamides, may be given synchronously. Practically no toxic or allergic reactions occurred in 50 patients studied for this report. Surgical lesions must be dealt with at the same time. Often only short duration of treatment is necessary, but weeks of treatment have been noted without the occurrence of toxic reactions.

NEUROLOGY AND PSYCHIATRY.

Psychiatric Casualties.

J. J. GELLER (*The Journal of Nervous and Mental Disease*, June, 1949) analyses a group of 480 army patients with psychiatric disorders. He finds that 57% showed predisposition to psychiatric illness prior to military service. The incidence was greater in women than in men, in spite of their lesser degree of military stress. There is a disproportionately large percentage of depressive psychoneuroses in women. Schizophrenia was the commonest type of psychosis; enlisted men tended to have the catatonic and officers the paranoid variety. Manic-depressive psychosis is three times more common in officers than in enlisted men.

Sexual Psychopaths and Shock.

G. N. THOMPSON (*The Journal of Nervous and Mental Disease*, June, 1949) has employed electroshock in six cases of sexual psychopathy. He concludes that convulsive shock therapy is of value in the treatment of psychosis with psychopathic personality, but that it does not alter the basic characteristics of the psychopathic personality; sexual psychopathy is not altered.

Toxic Psychoses.

THOMAS L. FOSTER (*The Journal of Nervous and Mental Disease*, July, 1949) discusses the relation of liver function and nutrition to toxic psychoses. Liver function tests were performed in a series of 51 cases. The author states that in a country in which pellagra is practically unknown, it is found that a relatively large number of patients with toxic psychosis have conditions clinically identical with pallagrous manifestations. These con-

ditions respond to the same treatment, namely, liver extract, brewer's yeast, "Ventriculin" and nicotinamide with adequate diet. Nicotinamide is given intravenously (300 milligrammes) for two days with 1000 milligrammes by mouth subsequently. It is contended that early treatment of the liver deficiency is important and must antedate electroconvulsive therapy or other measures. For sedation chloral hydrate is useful in mild cases; barbiturates are contraindicated, and paraldehyde is the sedative of choice. Heavy insulin-shock is contraindicated. The author feels that the term "toxic psychosis" is misleading and that a more descriptive term "nutritional psychosis" would be more appropriate for psychosis accompanying deficiency diseases.

Electroshock Therapy for Tuberculous Mental Patients.

BJARNE JENTOFT (*The Journal of Mental Science*, July, 1949) reports on 56 mental patients with pulmonary tuberculosis who received convulsive treatment. In 35 cases the pulmonary condition showed no change after convulsive treatment. In nine there was definite improvement. In 12 there was aggravation of the tuberculous process, but in nine of these the aggravation occurred so long a time after the conclusion of the treatment that a causal connexion is most unlikely; in the other three convulsive treatment may have had an unfavourable effect, but this is hardly more than might have been expected in tuberculosis cases of this type, even without any convulsive treatment, and it is therefore felt that pulmonary tuberculosis is no contra-indication against convulsive treatment. In depressed and agitated patients, who are poorly nourished and generally difficult to manage, benefit in relation to the pulmonary process will frequently result indirectly from the convulsive treatment because the mental state improves.

H. P. CLOSE (*The American Journal of Psychiatry*, November, 1949) believes that the high incidence of tuberculosis in mental hospitals is in part due to under-nutrition, hyperactivity of the patients, prolonged and intimate contact with active disease, and inadequate effort in finding active cases. He reports the cases of eight psychotic patients treated with electroshock therapy who benefited in relation to pulmonary tuberculosis after treatment, and this could indirectly be attributed to the electroshock therapy. The treatment of the pulmonary disease was conducted along the usual active lines and was supervised by a physician. The author states that electroshock therapy should be used if it is likely that it can particularly improve the cooperation, nourishment and bed rest of the patient.

The Cause of Deaths in a Mental Hospital.

H. JOSEPHY (*The American Journal of Psychiatry*, September, 1949) reviews the deaths in a large mental hospital over two periods, 1935-1937 and 1945-1947. He found that the rate of admissions had increased, particularly of patients over the age of seventy years, but the number of deaths during the two periods had not increased. The number of deaths from exhaustion in acute schizophrenia had greatly decreased, as had the number from general paresis; *delirium tremens* had disappeared as a cause of death. The author states that senile patients are becoming a special problem; a considerable percentage die soon after admission, while quite a number survive in mental hospitals for several years. With increased expectancy of life, more and more patients will live to the age of senile dementia, and a new social problem is developing which involves housing difficulties and care and supervision within the family.

Visual Agnosia.

A. ADLER (*The Journal of Nervous and Mental Disease*, January, 1950) discusses the course and outcome of visual agnosia. The discussion is based on a case of carbon monoxide poisoning acquired at the Cocoanut Grove disaster. The patient was then meticulously examined and has been followed up during the intervening five years. She is still unable to perceive the "whole", but can perceive "parts" without realizing their relationship. She is unable to calculate, and cannot copy block designs. In spite of her difficulties she leads a superficially normal life through an "amazing amount of round about ways of visual recognition". The author claims that this is a unique case.

Impulsive Wandering.

F. POLLAK (*The Journal of Nervous and Mental Disease*, September, 1949) describes the case of an English naval man, who for six years had irresistible impulses to wander away from his home. He would return in the early hours of the morning. "Pentothal" narcoanalysis revealed an extremely emotional episode in the battle of Narvik in which he had narrowly escaped death, and an incident in which his shell had killed a woman and child. As a boy of eight he had tried to kill his brother. After the narcosis, the patient said: "The load is off my chest." Six months later the urge to wander had completely disappeared. The author points out the persistence of the feeling of guilt and the probability that war neuroses must be regarded as re-editions of previous behaviour patterns. He draws attention to the short period of treatment, which did not preclude a dramatic recovery.

Lobotomy.

KURT GOLDSTEIN (*The Journal of Nervous and Mental Disease*, August, 1949) reviews the results of lobotomy and states that the chief finding lies in the loss of the quality of abstraction. The patient may appear normal in concrete situations, but is incapable of understanding and reacting to the abstract. The author points out that the power of abstraction cannot be learned; it is inherent. This has an important bearing on the use of lobotomy, which deprives a human being of a capacity which makes the essential of his personality. A careful evaluation of the structure of the personality of the individual patient, that is, his philosophy of life and of the conditions in which he lives and will have to live in the future *et cetera*, should precede any recommendation of the operation. It must be decided whether the improvement warrants the inevitable damage.

LAWRENCE C. KOLB (*ibidem*) gives a documented review of lobotomy. He summarizes the history of this operation and quotes 158 references. He concludes that whilst there appears to be good evidence that many chronically and hopelessly ill patients have been restored to community life, it is impossible to say how much of the improvement is due to surgery and how much to psychotherapeutic management. He asks the psychiatrists to copy the measures taken by surgeons in studying the treatment of cancer and suggests that the "five-year cure" should be adopted. In his opinion, the ability to evaluate properly this as well as other psychotherapeutic techniques begs for patience, the development of a more fundamental knowledge of the over-all course of personality disorders, more satisfactory means of stating the outcome of therapy than that presently used, and the insistence of psychiatrists as a group that therapy be judged on a realistic long-term basis rather than upon the hurried and preliminary impression immediately following termination of any particular procedure.

Depersonalization.

JEROME L. SAPERSTEIN (*The Journal of Nervous and Mental Disease*, September, 1949) discusses the factors underlying depersonalization, which he regards as an experience or impression of estrangement, involving the personality or self, the body or the environment—always with the more or less conscious awareness of the relationship of the estrangement to "a change in experiencing"; thus a patient notes the emptiness of his body, the loss of "sparkle" in himself, the difference in his voice, the automatic nature of his acts *et cetera*. The author states that the term depersonalization was first introduced by Dugas into the literature in 1848. Since then it has been shown to be present in numerous morbid states. The author presents it as a syndrome cutting across the diagnostic classifications of the personality disorders as well as being in the so-called normal. He holds that until it is regarded on broad lines and with a combined attack from every viewpoint, its true significance will be missed.

Genius and Psychic Abnormalities.

ADELE JUDA (*The American Journal of Psychiatry*, October, 1949) investigated the ancestors, relatives and descendants of 294 highly gifted personalities and the incidence of psychic disturbances amongst them. The investigation lasted seventeen years and involved the study of some 19,000 persons. No evidence was found to suggest that genius depends upon psychic abnormality. Mild psychic abnormalities within the limits of the psychoneuroses in some instances exerted a stimulating influence. There was a tendency for the genesis of high mental faculty to manifest itself in first-born and second-born children. Intellectual ability appeared to be manifest in the children and grandchildren. Mental deficiency was remarkably low, whereas the suicide rate appeared to be high. The schizoid constitution appeared to be prevalent among the artists, the cyclothymic among the scientists. The incidence of the corresponding psychoses was ten times greater than in the average population. The wives in the great majority of cases were excellent companions and appeared to contribute directly or indirectly to their husbands' accomplishments.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held at the Royal Alexandra Hospital for Children on April 18, 1950. The meeting took the form of a series of clinical demonstrations by members of the honorary medical and surgical staff of the hospital.

Congenital Heart Disease.

DR. S. G. BRADFIELD presented a boy, aged ten years, who had first been examined at the congenital heart disease clinic on March 20, 1950. The patient had two siblings aged six years and fourteen months respectively. His mother had had "kidney trouble" towards the end of pregnancy, but he was a full-term baby, born after normal labour, with a birth weight of seven pounds five ounces. A cardiac murmur was noticed at birth. He was slow to gain weight, sat up at the age of four months, walked at the age of two years, and was always thin. He walked without distress, but became breathless and developed blue fingers on running or climbing steps. Physical examination showed him to be thin, with clubbing and slight cyanosis of the fingers and toes. Femoral pulses were present. The liver and spleen were not palpated. The apex beat was palpable in the fifth left intercostal space in the anterior axillary line. A continuous humming murmur was audible, maximal to the right of the sternum and widely transmitted, especially to the back of the chest. A reduplicated first sound was heard, particularly towards the apex, with an accentuated first sound at the base, especially in the third left intercostal space. The blood pressure was 115 millimetres of mercury (systolic) and 90 millimetres (diastolic). The patient weighed three stone seven pounds ten ounces and his height was four feet four inches. The following X-ray report was made on February 16, 1950: "The cardiac shadow is enlarged. The enlargement appears to be mainly the right ventricle. There is an absence of fullness in the region of the pulmonary arc suggesting stenosis or absence of the pulmonary artery. The lung fields show normal markings. The aortic shadow is widened in all views and lies on the right side. The condition may be due to a Fallot, but is more suggestive of a truncus with a single ventricle and the pulmonary artery arising from the truncus. Angiocardiography would be advisable." The following electrocardiogram reports were made: "Sinus tachycardia. *P* waves peaked and high (2·5 mm.) in L2." "*P-R* interval above upper limit of normal range. Normal axis deviation. Wide *QRS* deflections. Consistent with certain forms of congenital heart disease, e.g., *truncus arteriosus*, single ventricle." Dr. Bradfield said that the condition was diagnosed as *truncus arteriosus* with pulmonary arteries arising from the base of the trunk. The pulmonary circulation appeared to be satisfactory, and there was no indication for surgical intervention.

Polycystic Disease of Liver and Kidneys.

Dr. Bradfield then presented a girl, aged six years, who had always been well except for bed-wetting. When she was examined at the out-patient department for that condition, abdominal masses had been found. Specific interrogation and physical examination revealed little of significance except that she was a pale, rather thin child, with a large mass in the liver area and two large masses, one on either side of the abdomen at the level of the umbilicus. Laparotomy revealed large masses on both kidneys and a large hepatic tumour. A biopsy specimen was taken from the liver and its examination revealed biliary cirrhosis. Dr. Bradfield said that both obstruction and infection appeared to play a part in the ætiology of the case under discussion. A possibility, suggested by the appearance of the bile ducts and warranting consideration, was that of congenital polycystic disease of the liver.

Pertussis Treated with "Chloromycetin".

DR. S. E. L. STENING presented a baby who had been admitted to hospital at the age of six weeks suffering from pertussis. The baby had been premature and remained in hospital for three weeks after birth. The baby's brother, aged two and a half years, had had pertussis for one week before the baby's admission to hospital. The baby had had a cold for three days and had begun to whoop and had four cyanotic spasms before coming to hospital. Examination revealed rapid respiration and rhonchi audible at both lung bases with crepitations in both lungs. In a spasm observed, cyanosis and apnœa appeared, the baby looked very ill and ceased breathing; immediate treatment was given with an oxygen tent and half a millilitre of adrenaline. A light growth of *Hæmophilus pertussis* was subsequently obtained from a post-nasal swab. Treatment was commenced with 50,000 units of penicillin, followed by 25,000 units every three hours to a total of 600,000 units. "Chloromycetin" was given in an initial dose of 0·25 gramme, followed by 0·125 gramme every eight hours to a total of 2·125 grammes. Oxygen and chloral hydrate were given as necessary. The baby had had 32 severe spasms with cyanosis, but only five short severe spasms since the completion of twenty-four hours' treatment. Numerous mild spasms occurred, including intermittent spasms since the baby's discharge from hospital; the mother stated that occasionally mild cyanosis was seen.

Cœliac Disease.

DR. D. G. HAMILTON presented a boy, a dissimilar twin, who had been referred to hospital in October, 1949, at the age of fifteen months, because of the frequent passage of loose, pale brown stools, failure to gain weight, occasional vomiting and irritability. His body, legs and buttocks were considerably wasted and his abdomen was distended. He was pale and his muscles were flabby. The stool was pale and bulky; 47% of it was fat, and of this 87% was split and 13% unsplit. A blood count revealed a total erythrocyte count of 4,600,000 per cubic millimetre, a hæmoglobin value of 8·2 grammes *per centum*, a colour index of 0·6 and a corpuscle index of 92; the leucocytes numbered 9700 per cubic millimetre, 67% being neutrophile cells, 29% lymphocytes and 4% monocytes. The boy was given a diet of low fat, high protein content, "Pentavite", seven minims three times a day, and ferrous sulphate one grain three times a day. His weight had slowly increased, his motions had become normal, except for an occasional bout of diarrhœa, and his hæmoglobin value had risen to 10·9 grammes *per centum*.

Rickets.

Dr. Hamilton's second patient was a boy who had reported to hospital at the age of two and a half years, in July, 1948, with severe bow legs, muscle hypotonia, a prominent abdomen and Harrison's sulcus. X-ray examination revealed severe rickets. He was given "Potantol", ten minims, three times a day, a diet of high protein, low carbohydrate content, night splints and exercises. In March, 1949, the radiologist reported that the bone changes were characteristic of renal rickets and still unhealed. There had been no decrease in the bowing of the legs, but the child looked well and muscle tone was normal. The findings from microscopic and chemical examinations of the urine, the blood urea content and the result of the urea concentration test were all normal. In August, 1949, he was given a heel built up on the inner side and extended under the instep. In December, 1949, the X-ray picture still suggested unhealed renal rickets. The dose of "Potantol" was increased to thirty minims three times a day. A number of abscessed teeth were removed, and his general health improved as a result. However, his plasma alkaline phosphatase value was still 65 King-Armstrong units, indicating that the disease was still very active.

Achondroplasia with Hydrocephalus.

DR. S. E. J. ROBERTSON presented a female child, aged three years and eleven months, who had been born at full-time gestation after a normal pregnancy, weighing six pounds four and a quarter ounces. The delivery was complicated by a brow presentation and instruments were necessary. The baby's condition was unsatisfactory for the first few weeks of life owing to partial atelectasis of the left lung. She was first examined at the out-patient department when three months old. She then weighed nine pounds thirteen and a quarter ounces, had a large head with a circumference of 17 inches, and was slow in movement with poor joint tonus. Mild hypochromic normocytic anæmia was present. She was admitted to hospital for investigation, and radiological studies revealed achondroplasia of the long bones with an enlarged head and a shallow, bilocular pituitary fossa suggesting hydrocephalus. A pneumoencephalogram was prepared, which revealed mild dilatation of the right lateral ventricle and large, fluid-filled spaces on the cortex suggesting *agenesis cerebri*. It was thought at that time that the hydrocephalus was partly compensatory and partly due to shortening of the base of the skull and kinking of the *aqueductus cerebri*. The child was returned to the out-patient department and examined at regular intervals. The head continued to increase in size and reached its maximum diameter of twenty-one and a half inches at the age of thirty months. The child sat up unsupported at twenty months, stood up with support at twenty-

five months, and walked unsupported at thirty-eight months. The laxity of all joints remained the same, and *genu valgum* appeared when she stood up. At the time of the meeting the child was eating well, but had not yet attempted to talk. The trunk was of normal length, but the limbs were short, especially in their proximal portions. The muscles were soft and had diminished tonus. Pronounced *genu valgum* was present. The buttocks were prominent with considerable lordosis. The hands were short and broad, and the fingers exhibited the trident appearance. The head was brachycephalic and large with a bulbous frontal region. The face was small with a depressed roof of the nose. Dr. Robertson commented that the questions raised by the case were whether the failure to talk was due to cerebral damage and whether speech therapy was likely to succeed. It was proposed to repeat the pneumoencephalogram to see if the changes in the cerebral cortex were still present.

Cavernous Hæmangioma.

DR. HENRY SHARP presented a series of patients with cavernous hæmangioma treated by superficial X-ray therapy. The nævi had been exposed to fractional doses of 200*r* at two-weekly intervals. Four treatments were given initially, and, depending upon the progress made, a second course of two to three exposures was ordered after a rest period of three months. That dosage was found sufficient to cause total regression of the lesions in eighteen months to two years. For scalp lesions, a dose of 400*r* was given initially and repeated in one month. Rarely a third exposure was found necessary. Temporary defluvium took place, but ultimate hair-growth was excellent.

Dr. Sharp summarized the various methods of treatment and discussed their advantages and disadvantages. The following advantages were listed for superficial X-ray therapy: (*a*) the final results were of a high cosmetic standard; (*b*) the treatment was painless and no anæsthesia was required; (*c*) admission to hospital was unnecessary; (*d*) the penetration of the X-ray beam was readily controlled by varying the quality of the radiation, and that, combined with divided dosage, prevented damage to underlying structures such as epiphyses; (*e*) complete hair-growth followed the treatment of scalp lesions. The necessity for early treatment was stressed, and six weeks to two months was suggested as the optimum age at which to commence X-ray therapy.

(To be continued.)

Special Correspondence.

LONDON LETTER.

FROM OUR SPECIAL REPRESENTATIVE.

"For This Relief, Much Thanks."

FOOD GIFTS worth £80,000,000 have been sent to Great Britain by the peoples of the Commonwealth and the United States of America, and, in gratitude for this generosity, the Lord Mayor of London has opened a National Thanksgiving Fund, the proceeds of which will be spent mainly in providing more residential accommodation in London, along the lines of London House, for use by students coming from overseas. The inaugural meeting, at which Princess Elizabeth was the chief guest, took the form of a dinner at the Guildhall and was accompanied by all the pomp and ceremony, vocal and visual, which attend City of London functions. The broadcast description was wisely entrusted to a woman commentator, who was on her own ground when describing the dresses of the ladies, the gorgeous robes of the city dignitaries and officials, and the table decorations, floral, edible and civic. All this colour made a fine show against the grey walls of the Guildhall, still bearing marks of enemy action, but with Dick Whittington's window unharmed in one corner. The Lord Mayor described the sending of the parcels as "an action of generosity written in the pages of history" and mentioned that already one-fifth of the sum aimed at was promised. The pleasant and sincere voice of Princess Elizabeth came over well, and she said that 140,000 food parcels had been made up and distributed from the gifts she had received on the occasion of her wedding. The sum aimed at is £2,000,000, and her comment was: "This may seem large, but it is no less large than the bounty it is to commemorate." The Prime Minister thought that the fund would meet two needs—it would express gratitude and would benefit visiting students. Mr. Churchill, who received a very warm welcome, felt that the Guildhall, "scarred by the wounds of conflict", was an appropriate place to launch such an appeal which would be of benefit to people overseas to whom so much was owed both now and during the years of war. He concluded, "I agree with all the Prime Minister has said", paused a couple of seconds, and then added the qualification "tonight". It was an historic occasion and a colourful scene. The main object of the fund is to provide suitable accommodation for students coming from overseas at prices they can afford. The buildings will be near London House, which now provides collegiate life for some 220 men students from the Dominions and colonies and which stands on the south side of Mecklenburgh Square. It is proposed to build a residential hall on the war-damaged north side of the square for women and married couples and to adapt some of the fine Georgian houses on the east side chiefly for men students from the Commonwealth and from the United States. The remaining side is a permanent open space. Every effort will be made to retain the architectural amenities of the square. At the same time £150,000 has been earmarked for "The Burn" a residential mansion in Scotland used by overseas students and run as an offshoot of London House. The new buildings and London House will be administered under the one organization and £600,000 will be set apart to provide for their upkeep. If funds permit, grants will be given to the Overseas League, the Victoria League, the Royal Empire Society, the Dominions Fellowship Trust and the English-Speaking Union, which have done so much in providing and arranging private hospitality for visitors from overseas.

As may be imagined, a project of this size has to meet with criticism. An early one was that, though the fund claimed to be national, its benefits were limited to one square in London, a mansion in Scotland, and to a certain extent to the University of London. Civic, and to a less extent university, authorities in the provinces felt some diffidence in being asked to collect money for a scheme the benefits of which would be centred in London. The Lord Mayor of one midland city which possesses a fine university declined to sponsor any local collection in his civic capacity, but softened his attitude by heading the subscription list in his own city. A professor in an American university, who has worked in this country, pleaded for a better knowledge overseas of provincial universities in the United Kingdom. "Few students abroad recognize, as they should, the place of, say, the University of Sheffield in the field of glass technology, or Leeds University in textiles, or the University of Liverpool in architecture." Another reason for a wider distribution of favours was put as follows: "If anyone who sent us parcels comes to our city, I want to be able to show him something and say that is the sign of our gratitude." The domiciliary segregation into Dominion, American men, women and married couples has occasioned some criticisms mainly from American sources. "It would be most ideal for American students to be admitted to hostels peopled by English students, not only in London but in the provincial universities." Against this, an American professor with thirty years of academic experience in this country feels that the fund will prove of incalculable benefit to those students whom it is designed to serve. Most American students, he points out, will be graduates of senior standing who come to London for a definite purpose and whose work will bring them into contact with English teachers and students and who will be eligible to join students' clubs and associations. In selecting the site for the new buildings, the presence of a fine nucleus in London House, with a wealth of experience and goodwill behind it, and the lure and lore of London are compelling factors. The students from overseas who will not spend some at least of their time in London will be few in number and the majority will spend much of their working time there. A proportion will naturally work in Scotland or the provinces or under particular teachers, but it will be to their advantage to have an experienced and friendly headquarters in Mecklenburgh Square to which they can turn should need arise, more particularly before and in the days following arrival in the United Kingdom.

The needs of students coming from overseas were sympathetically and wisely dealt with in a recent excellent broadcast by the Warden of London House, Brigadier Pepper. In his opinion the visitor deserves a welcome, will probably want advice on educational problems and will wish to see places and meet people over and above those he comes in contact with in his work. If past experience is any guide, the enlarged centre will be able and ready to help in these difficulties whether the newcomer is to work in London or elsewhere. The collegiate system makes for contacts and friendships with men from other parts of the English-speaking world, and the object of the fund is to make such facilities available not only to a greater number, but also to a wider range of visitors. As far as medical matters are

concerned, the present close liaison with the Empire Medical Advisory Bureau at nearby British Medical Association House will continue. The Warden of London House is an active member of the Board of Management of the Empire Medical Advisory Bureau.

The feelings of many people on the question of site are best expressed by one correspondent who, after referring to what he regarded as quibbles over details which did not interest him, summed up: "I have, however, a very profound feeling of thankfulness to the Lord Mayor in that he has provided some means for us to show, in a tangible form, our extreme gratefulness for all those wonderful parcels from our friends in the Dominions and that is all that really matters to me." Gifts have ranged from £50,000 to sixpence: the oldest contributor is a woman of ninety-seven, the youngest a boy and a girl, each of five years. Many old-age pensioners have sent to the fund, and at first the initials "O.A.P." coming after the name led to some doubt as to what they stood for. Now they are so part of the day's mail that their absence would occasion surprise. Three sisters, all under nine years of age, living with their widowed mother, sent a postal order for 1s. 6d. and 1s. in stamps and wrote: "Although you do not mention orphans we hope it will be all right." Now, as we enter "Thanksgiving Summer in Britain"—so different from summer ten years ago—we are all sure "it will be all right": Britain is saying: "Thank you."

"Teething Troubles."

In an earlier letter (THE MEDICAL JOURNAL OF AUSTRALIA, April 22, 1950, page 549) attention was drawn to the difference between the estimated and actual cost of running the National Health Service. Both the Minister of Health and the Chancellor of the Exchequer have spoken strongly on this subject and the former has given a pledge that the financial ceiling laid down for 1950-1951 will not be exceeded. Money overspent in one direction must be compensated for by an equal saving on another and less urgent item; a uniform system of accountancy is to be introduced into all hospitals so that any extravagance can be quickly brought to light and dealt with. The size of staffs is to be laid down by a visiting team consisting of administrative officials and members with a medical background and a knowledge of hospital administration. The Minister's intention to keep within the estimates may be quite sincere, but once bitten twice shy, and the taxpayer will be inclined to suspend judgement till the final figures are known. Dentistry is probably the most lucrative form of service under National Health Service, and some of the incomes earned sound fantastic. The record appears to be held by a Scottish dentist, employing one assistant, who was authorized payment of £18,077 for the period July 5 to December 31, 1948. This was too good to last, and in June, 1949, dentists' fees were dropped by 20%, and another cut of 10% has just been made. This recent unilateral action by the Ministry is resented by the British Dental Board, who feel that there is no useful purpose in continuing negotiations on remuneration. A dental Member of Parliament admitted in a House of Commons debate that the cost of the dental service was running as high as, if not higher than, the general medical service, though there were only 9000 dentists as compared with 19,000 medical practitioners. The recent cut he felt was right, but the method of making it was wrong, for the slow but good worker would suffer just as much as the less scrupulous man making as much as he could. A sliding scale would have been wiser, say 2·5% on gross earnings of £450 a month, 10% on £500 gross and so on. An increase in the number of inspectors was urged, as less than 0·5% of the estimates were referred for inspection, though the average amount of saving on the cases examined was 20%. For the Ministry it was pointed out that the Spens report recommended an income of £1,800 a year as against the average income of £2,250 now being received by dentists after expenses had been allowed for. It was generally agreed that there are too few dentists and the Government must decide which patients were to come last, or at least which were to come first. One result of this gross initial miscalculation as to rates of pay and amount of work presenting is that the number of dentists doing private consultant work has increased, mainly at the expense of services run by government departments and local authorities and, in particular, the dental service for schools and school-children, which has been described recently as "one of the real casualties of the National Health Service". This service has never had a recognized salary scale, has always been short of trained personnel, and since the inception of the National Health Service the number has dropped by about one-third. Various suggestions have been made to deal with the steady and considerable deterioration in the condition of the school-children's teeth. One proposal was that every dentist should be compelled to treat a certain number of children, but such consultations would be difficult to arrange. A trial is now being given to a method of treatment for dental decay which has a certain vogue in the United States, but which was not greeted with any great enthusiasm at a recent dental congress held here. With the written consent of their parents, some 3000 children throughout the country are to have their teeth painted with sodium fluoride: the Ministry claims that there is less dental decay in areas where this drug is present in the drinking water. The application is painless, does not leave any stain, and the effect is said to last up to three years. The reaction of the dentists to their latest cut remains to be seen, but there are signs of other financial storms brewing. The doctors are asking for the full implementation of the Spens capitation rates of pay, and since the extra tax of ninepence per gallon has been put on petrol, a request for special treatment for doctors is being made to the Chancellor: the rural practitioners will be the hardest hit by the extra cost of petrol, that is the group which has had the biggest drop in income. Some 600 doctors in the Education, Health, Labour, National Insurance, Pensions, and Prison Medical Services, after having requests for increases in pay refused, asked through their Joint Committee for an interview with the Chancellor and were refused. They are to repeat the request and have asked that in the meantime the *British Medical Journal* should not publish advertisements for Civil Service medical appointments. Prescribing is being closely looked at and doctors are being asked before prescribing an expensive preparation to decide: "Am I satisfied that a standard drug or combination of standard drugs cannot be prescribed with equal effect?" Reference has been made to the disturbing fact that only a small part of the cost of the National Health Service is being spent on reequipment, new buildings and the like, the main part going in running expenses: this is due partly to a national rise in salaries and cost of living. It has been stated that a certain teaching hospital in London, run efficiently pre-war on £125,000 from voluntary subscriptions, "now needs one and a quarter million of taxpayers' money to keep its doors open". The sober facts set out above could be added to, but enough has been written to show the need for caution and proceeding a step at a time when embarking on such a project as a national health service.

"What's in a Name?"

In preparation for next year's Festival of Britain, buildings are being erected and the river bank strengthened along that part of the Thames generally known as the South Bank which runs from the County Hall near Westminster Bridge to Waterloo Bridge and which faces the Victoria Embankment on the opposite, or Strand, side of the river. Some little time ago a writer to *The Times* suggested that a more suitable name than South Bank might be found, and later correspondents have approached the problem from different angles, historical, geographical, descriptive, and at times a combination of these. In Elizabethan times the Globe, the Rose and the Hope Theatres, the Mermaid Tavern and various places devoted to bull and bear baiting were located in this vicinity, and, from this association, names such as Mermaid Reach, Shakespeare Shore and Shakespeare Embankment have been suggested. As the area was a playground in those days and is to be a playground once more, Festival Gardens might be appropriate and would commemorate the Festival of Britain as Crystal Palace does the Great Exhibition of a hundred years ago. Again, in the early part of the eighteenth century, a well-known, though not particularly reputable, pleasure ground flourished on or near the present site and the name of Cuper Gardens is put forward in memory of Bodwin Cuper, who presided over the earlier place of amusement. Shot Tower Hall is proposed in order to commemorate a long-established and well-known architectural feature of the area and would carry on the custom seen in such names as Birdcage Walk, Temple Lane, Horse Guards Avenue and Printing House Square. From the purely geographical angle we get Surrey Strand or Side, Lambeth Embankment, Hoe or Shore, Waterloo Bank or Shore and Southward Staith (Anglo-Saxon for landing stage). As Watling Street, the earliest crossing from London into Kent, ran near by, Watling Wall is suggested. A number of people feel that any change of name should be linked in some way with the Victorian Embankment on the opposite side of the river and propose Empire or Elizabeth Embankment, the latter as it refers to perhaps Britain's greatest Queen, the present Queen, and our future Sovereign. As against this, one correspondent pleads for the omission of the word "embankment, surely one of the ugliest words in the language". A light touch is given to an otherwise serious discussion by a letter signed G. Bernard Shaw, which advocates the word "bank" rather

than "embankment" on the score of the former having fewer letters which would "effect a saving of manual labour that will soon run to millions of saved hours". A brother humorist, Sir Alan Herbert, writing over the signature Alan H., points out that under this "queer letter saving system" Waterloo Bridge would appear as Bridge W. and goes on to ask what of "G. Bernard Shaw? Why Bernard? Seven letters. What a waste of man hours and letter miles". St. George's Field has a fine patriotic and loyal ring, and the suggestion of Jenkins is in memory of Sir Leoline Jenkins, who in 1685 left a large part of this bank of the Thames to Jesus College, Oxford. When bridges were few and far between landing places were more numerous and the King's Arms Stairs was a well-known one. On the theory that the new name should bear some relation to the river, rather than to the land behind it, and also have some link with the past, The King's Stairs has been proposed. A gentleman with a strong political bias suggests commemorating the present Government by the name Rakes' Progress. If a guess has to be made as to the final choice, continuance of South Bank seems the most likely, particularly as some meticulous geographers have pointed out that the Thames runs north-south at the stretch concerned, and, if topographical accuracy is to be a deciding factor, east is to be preferred to south. The average Londoner rather likes this type of nomenclature which does not mean exactly what it says: a case in point is Ludgate Square, which is a narrow twisting passage about the length of a cricket pitch. A *Times* leader, reviewing the correspondence, ends with the words, "Why not South Bank?", and one of the few women contributing to the discussion shares this view and writes: "It will scarcely lighten the difficulties of the visitor struggling with the complexities of London topography if his inquiries for Waterloo Walk or Shakespeare Shore are met with blank looks and the eventual reply, 'Oh, you mean the South Bank!'"

"In Lighter Vein."

Gallery talk. The new Minister of Food has promised to call what we eat, food, and not Calories.

The Minister of Food
Already earns his salary:
For has he not eschewed
All playing to the Calorie?

Correspondence.

SMALLPOX, VACCINATION AND THE QUARANTINE SYSTEM.

SIR: At the recent meeting of the National Health and Medical Research Council, held in Sydney on May 17 and 18, 1950, the Council considered the increasing risk of smallpox entering Australia, and at the request of Sir Earle Page, Minister for Health, discussed the desirability of varying the use of quarantine stations throughout Australia.

The Council passed the following resolutions:

> The Council is impressed by the very greatly increased risk that Australia is now facing in the introduction of smallpox and other quarantinable diseases because of the vast development of air traffic and the greatly increased speed of sea traffic from countries which at the present time are suffering from widespread epidemics of these diseases.
>
> The Council is entirely opposed to any suggestion of interfering in any way with the present quarantine stations and with the present system of quarantine, as it is of the opinion that this would endanger the public health of Australia. The Council strongly believes that the Commonwealth should not relax any of its present methods of quarantine, and is of the opinion that the introduction of any other system would inevitably increase the risk of spread of outbreaks of smallpox in this country.
>
> This Council, having considered the possibilities of the entry of smallpox into Australia from Asia, urges as an immediate precautionary measure that all persons likely to be exposed if a case of smallpox develops unexpectedly should be vaccinated, with revaccination at the end of three years. This group would cover medical practitioners, medical students, employees of hospitals, ambulance employees, health inspectors, persons employed in aeroplanes and on aerodromes, policemen, wharf labourers, taxi drivers, crews of Australian vessels, employees of shipping companies who come in contact with overseas traffic, Press reporters, pilots and all persons who are likely to come in contact with overseas vessels.
>
> The Council recommends that each State should encourage voluntary vaccination throughout the community of young children between the ages of three months and two years and urges the desirability of revaccination when the child enters school. School authorities should be encouraged to ask for vaccination certificates before the child enters school.

It is thought that these resolutions might be of general interest to the profession and it would be appreciated if you could arrange for publication.

Yours, etc.,
A. J. METCALFE,
Director-General of Health.

Department of Health,
Canberra,
June 6, 1950.

LONDON MISSIONARY SOCIETY: AN APPEAL FOR WOMEN DOCTORS.

SIR: I should be grateful for the opportunity of making known through your columns the need of the London Missionary Society for women doctors in three of its well-established hospitals in India. These are at Neyyoor and Erode, South India, and Jiaganj in Bengal. Nurses' training schools are attached to the first two.

Information in regard to all three appointments will gladly be given to any who may wish for particulars.

Yours, etc.,
ELEANOR RIVETT,
Honorary Woman Secretary for
Australia and New Zealand.

Chalmers House,
41 The Boulevarde,
Petersham,
New South Wales.
June 13, 1950.

ANTIHISTAMINES IN PREGNANCY.

SIR: I would venture to say that nausea and vomiting in early pregnancy have been symptoms which have caused all obstetricians anxiety at times. Therefore, I would like to record briefly my own recent experiences.

Since August, 1949, I have treated 75 women presenting themselves between the sixth and fourteenth weeks of pregnancy for nausea and vomiting in which no factor appeared to be present to account for the symptoms except the pregnancy. The majority of these women were less than ten weeks pregnant, and the severity of the condition varied from severe nausea to "vomiting everything all day". No case was hospitalized.

I have given all these patients antihistaminic drugs, and have been truly amazed at the results. Not one patient has failed to respond to treatment, and they responded within one to three days for the most part. Seventy-two were completely relieved, and the other three were completely relieved except for slight nausea after taking meals containing a large amount of fat.

I have found no difference in response with any particular brand of drug, and the following trade preparations have been used: "Antistine", "Diatrin", "Trimeton", "Benadryl", "Phenergan" and "Pyribenzamine". The maximum dose of any drug used has been 300 milligrammes per day, but some have been relieved by much smaller doses. Once relief has been obtained, I tell the patient to gradually reduce the dose till she has found the minimum dose necessary to keep her well. Having found this apparent minimum, I tell her to take this for three days and then start reducing again. A few patients have required treatment for as much as two months, but several find that once relieved they can go on reducing the dose to nothing and relapse does not occur. Those who have relapsed have all been relieved by retaking the drug. There have been no ill effects on the mothers or the babies so far delivered.

I offer these remarks in this way without statistical analysis, for what they are worth, and in the hope that they will stimulate some comment. I hope to be able to present a bigger series in detail later.

In these cases no other treatment designed to assist the cure of the nausea and vomiting was given.

If these drugs prove to be as effective as this always, does it shed any light on the ætiology of this condition?

There is one other observation I would like to make concerning these drugs. I have used them in a small number of cases of preeclamptic toxæmia with albuminuria, and I have the impression that these cases were benefited. The albumin promptly disappeared and no case became worse. In these cases the other usual methods of treatment were employed at the same time, but the response seemed to be better than usual, especially as the cases selected for treatment with these drugs were ones which I suspected were likely to run a downhill course. I know this last is a very vague statement, but this experience is quoted in the hope that someone with more cases than I can give me some information on their results, if they have already used this method, or may be led to give it a trial under more controlled conditions.

Yours etc.,

R. CECIL BLACK.

Old Cleveland Road,
Camp Hill,
Brisbane.

June 3, 1950.

A MORE REALISTIC VIEW OF TUBERCULOSIS.

SIR: I have been interested in the correspondence on this subject which has recently appeared in your columns, especially as many of the problems raised are those for which one has been seeking an answer. I would believe, however, that Dr. Short's remarks create a wrong impression. The subject of tuberculosis is most puzzling, and the handling of tuberculous patients is beset with difficulties and pitfalls, but I cannot see that Dr. Short's letter in your journal on May 27, 1950, has clarified the position, or put forward anything like a realistic view, unless it be the realism of the ostrich, who with his head beneath the sand, can see no storm, or of the cult of Mrs. Eddy, which believes that diseases such as pulmonary tuberculosis have no basis in fact, that they are the imaginings of our minds, or, as Dr. Short would suggest, the artefacts of our machines.

The letter itself is confused and confusing, but I take it that the chief point is that some shadows found radiologically are misdiagnosed as pulmonary tuberculosis, and that others are possibly correctly diagnosed but improperly treated. Both these assertions are true in certain cases, and the consequences (as Dr. Short points out) are harmful—so is any misdiagnosis or maltreatment! Before the days of mass X ray one has seen cases similarly misdiagnosed, as, for instance, that of a young woman, aged thirty-two, who had spent twelve years in and out of sanatoria on account of recurring hæmoptyses, but with no bacterial confirmation of the diagnosis. The cause of her symptoms was, in fact, a localized and otherwise symptomless area of bronchiectasis. We would agree that it is just as harmful to diagnose tuberculosis when it is not present, as to miss an early case whether that diagnosis is made on symptoms or on radiological signs. This does not mean that we should ignore either the symptom or the sign, but should redouble our effort to establish the correct diagnosis. The greatest assistance is given by the bacteriologist; but sometimes he gives us no positive answer, while the bronchoscopist and bronchographist give us no help, and in these cases the diagnosis has to be made on the "life history" of the disease process as seen in serial films. This life history is none the less real because only seen in shadow form on radiographic plates, instead of a progression of symptoms and physical signs, as, for instance, in disseminate sclerosis.

We have all seen mass radiography misused, as, for instance, people refused employment because of some very dubious variation in the film, later shown to be of no significance whatever; but in spite of such happenings, the use of X rays remains the most useful method of case finding in pulmonary tuberculosis which we possess and should be used widely but with due care and judgement.

The assessment of activity is sometimes difficult, as your writer points out, but surely no one attempts this assessment on one film alone. The symptoms, temperature chart, sputum examination, sedimentation rates *et cetera* complete the picture. There are some cases, however, in which all these are normal, and yet serial X rays reveal sure evidence of extension of the disease. By these means we can gain some idea as to which cases require treatment and which observation. Dr. White has already pointed out that quite a large number of these active cases have insignificant symptoms. Dr. Short seems to argue that because some cases will recover whether or not they are given treatment, that all symptomless cases should have no treatment. The point seems to be that at present we cannot tell which cases will go wrong and therefore feel that all active cases should be treated. I suppose the majority of cases of acute appendicitis would subside if treated conservatively, but early operation on all is indicated because we cannot distinguish between those which will resolve from those which will perforate. I think we should emphasize, too, that what are apparently inactive lesions may light up at some future date, and that the first evidence of this may be radiological—hence the wisdom and realism of observation and follow-up.

Unfortunately Dr. Short has drawn across the trail a large red herring in the shape of repatriation pensions. This has clouded the issue in the past, so that what has obviously been a tuberculous focus has been labelled "pulmonary fibrosis" (often, I suspect, with tongue in cheek), as there were no symptoms and no bacteriological proof. These cases have therefore not been followed up because not entitled, and one has seen numbers of such cases only after the progressive damage is beyond repair. As medical men we should state the diagnosis as accurately as we can. The same problem arises with primary pleurisies with effusion, which are nearly all tuberculous, and the patient requires an adequate follow-up, although three-quarters may have no further trouble. Personally, I do not believe these people should have a pension for life, but we must state our diagnosis: "Primary pleurisy with effusion, almost certainly of tuberculous etiology; he requires a period of sanatorium treatment, and follow up for five years thereafter." Most are accepted for pension purposes as "pulmonary tuberculosis". We should not dodge the true diagnosis because we disagree with certain regulations.

Dr. Short appears to confuse symptomless infections in adults with primary infections; most of them are not. If, however, he is interested in what happens to primary infections in adolescents he will find some of his answers in the writings of Heimbeck (1936) and in the Prophit survey (Daniels *et alii*, 1948). In brief, a primary infection in an adolescent is more likely to result in a progressive parenchymal lesion than such an infection in childhood, and such disease generally manifests itself in close connexion with the primary infection. This is therefore a critical period in the lives of these patients and they require most careful management. Those who have to do with such groups as hospital nurses will find adequate verification of these statements.

I write this letter, sir, as I feel that Dr. Short has a "half truth", but he has stated it in such a way as to be misleading and destructive, and far from realistic. We all know we have not all the answers. The battle against tuberculosis is on, and in any battle reconnaissance is most important; we want to know where the enemy is, and what his movements are. Our observations and deductions may at times be false or uncertain, but what general would do without his intelligence service? Mass X rays provide one method of reconnaissance, and it must be used widely and skilfully.

There are hopeful signs that the battle will be won, although there are inevitable setbacks and disappointments, but do not let us get right back to a fatalistic, defeatist attitude because we do not yet understand all the vagaries of the disease, but rather, with robust hopefulness, stand behind those who are at present directing operations.

Yours, etc.,

J. ERIC CLARKE.

12 Collins Street,
Melbourne,

June 15, 1950.

References.

Daniels, M., *et alii* (1948), "Tuberculosis in Young Adults", Royal College of Physicians Report on the Prophit Tuberculosis Survey, 1935-1944. London: H. K. Lewis and Company, Limited.

Heimbeck, J. (1936), "Tuberculosis in Hospital Nurses", *Tubercle*, Volume XVIII, page 96.

THE USE OF "SODIUM PENTOTHAL" ADMINISTERED CONTINUOUSLY IN ABDOMINAL SURGERY.

SIR: I feel bound to comment on the article of Dr. Fowles on "Pentothal" anæsthesia in the issue of June 10, as I feel certain that many of his comments are not the opinion of anæsthetists as a whole.

The danger of "Pentothal" actually varies with the skill and experience of the administrator. Hence the saying "dead easy, easy dead". "Pentothal" *per se* is not a toxic or dangerous drug.

As regards the relaxing property of this drug, as a general rule I would say it is bad and in most cases can only be obtained with overdosage.

Dr. Fowles's claim to relieve laryngospasm by intubation is a complete misconception. With the exception of the administration of a relaxing agent, this condition is only relieved by the removal of the initiating stimulus or terminal asphyxia. In Dr. Fowles's case it would appear that terminal asphyxia relaxed the cords, when intubation would be unnecessary and a waste of valuable time. I suggest that "mouth to mouth" inflation with the aid of a rubber mask would have been a better procedure. To my mind laryngospasm is caused by irritation to the cords from any cause and appears under any anæsthetic which irritates the cords. "Pentothal" and ethyl chloride, which appear to enhance parasympathetic activity, are well-known offenders and only "predispose" to the condition.

Dr. Fowles's impression that one one-hundred-and-fiftieth of atropine is better prophylactically than one one-hundredth of atropine must surely be a false impression, as the purpose of the drug is to inhibit vagal action. The larger dose from a pharmacological viewpoint must be better.

Intranasal oxygen with a catheter at flows of two to four litres per minute I consider useless, and only likely to disturb the anæsthetic. These flows will only increase the oxygen content of the inspired air to barely 30%. A far better procedure is the use of an oro-nasal "B.L.B." mask with a flow rate of five to six litres per minute.

In contrast to Dr. Fowles's opinion of the increasing pallor met with during "Pentothal" anæsthesia, I take this as an indication to stop the drug, as it is due to profound depression of the cardio-vascular system, a condition incompatible with good anæsthesia. With regard to the therapeutic use of "Pentothal" in hypertension, I would remind Dr. Fowles that using radioactive "Pentothal" it has been found that a normal dose of "Pentothal" is completely excreted within seven days.

An especially dangerous comment was: "If cyanosis persists in the presence of oxygen, then a change should be made to some other type of anæsthetic." Obviously if this condition occurs under any anæsthetic, the airway or ventilation of the patient is at fault. Full tracheo-bronchial toilet should be carried out, and assisted breathing or artificial respiration instituted at once.

In conclusion, Dr. Fowles's "post-operative 'Pentothal' intoxication" is sheer nonsense. This "condition" occurs in any patient in pain under the influence of an hypnotic drug such as "Pentothal" becomes during the emergent period. An analgesic drug such as morphine quickly relieves this so-called condition.

With all due respects to Dr. Fowles's wide experience of "Pentothal", I feel his opinions are based on false premises and an inadequate experience in the use of other agents.

Yours, etc.,

13 Gilbert Park,
Manly,
New South Wales.
June 13, 1950.

L. E. McDONNELL.

Royal Australasian College of Surgeons.

GORDON CRAIG SCHOLARSHIPS.

THE Council of the Royal Australasian College of Surgeons invites applications for the seventh award of Gordon Craig scholarships.

1. These scholarships are awarded for the purpose of furthering post-graduate education in surgery and surgical research.

2. Favourable consideration will be given to applicants who intend to present for a senior surgical qualification.

3. Applicants must have been qualified for at least two years.

4. Scholarship holders will be required to carry out whole-time duty at a medical school and/or research institute and/or hospital, although this condition may be varied in exceptional cases.

5. The amount of each scholarship will be at the discretion of the College, but the College is prepared to grant up to £400 a year to suitable applicants.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JUNE 3, 1950.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[2]	Australian Capital Territory.	Australia.[3]
Ankylostomiasis	*	..	..	..	4	..	..	..	4
Anthrax	*	..	..	..	..	..	..	..	..
Beriberi	*	*	*	*	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	..	1(1)	..	..	1(1)	..	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	..	*	*	*	*	*	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	1	..	..	..	..	..	1
Diphtheria	12(4)	6(5)	2(2)	1(1)	3(3)	..	..	..	24
Dysentery (Amœbic)	*	..	..	..	1	..	..	..	1
Dysentery (Bacillary)	*	6(6)	2(2)	..	6	..	..	..	14
Encephalitis Lethargica	..	..	1	..	..	..	..	..	1
Erysipelas	*	*	*	2(1)	*	*	..	..	2
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	..	*	*	..	*	*	..	..
Influenza	*	*	*	..	*	*	..	*	..
Lead Poisoning	*	*	..	*	*	*	*	*	..
Leprosy	..	..	..	..	..	..	..	..	..
Malaria(*b*)	*	1(1)	..	..	1	..	..	..	2
Measles	*	*	*	21(16)	*	*	..	..	21
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	9(4)	2	1(1)	14(11)	2(2)	..	..	..	28
Psittacosis	*	..	*	..	*	*	*	*	..
Puerperal Fever	..	..	..	..	1	..	..	..	1
Rubella(*c*)	*	*	..	*	1(1)	*	..	..	1
Scarlet Fever	11(7)	24(19)	2(1)	18(15)	5(2)	2(1)	..	..	62
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	..	1(1)	*	*	*	*	*	1
Trachoma	*	..	*	*	*	*	*	*	..
Tuberculosis(*d*)	18(14)	6(5)	13(9)	5(3)	16(9)	3(1)	..	..	61
Typhoid Fever(*e*)	1(1)	..	..	..	..	..	..	..	1
Typhus (Endemic)(*f*)	..	..	5	..	2(2)	..	..	..	7
Undulant Fever	..	..	2	..	..	..	..	..	2
Weil's Disease(*g*)	*	*	1	*	*	*	*	*	1
Whooping Cough	*	*	*	1(1)	*	*	..	..	1
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 37, 1946–1947. Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from the Northern Territory.
* Not notifiable.
(*a*) Includes Mossman and Sarina fevers. (*b*) Mainly relapses among servicemen infected overseas. (*c*) Notifiable disease in Queensland in females aged over fourteen years. (*d*) Includes all forms. (*e*) Includes enteric fever, paratyphoid fevers and other Salmonella infections. (*f*) Includes scrub, murine and tick typhus. (*g*) Includes leptospiroses, Weil's and para-Weil's disease.

6. Forms of application, together with details of the regulations governing the award of the scholarships, are available from the secretary of the Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1.

7. Applications should be lodged with the secretary and reach him not later than January 31, 1951.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that the lecture to be given by Professor Francis G. Blake at Sydney on Friday, June 30, at 8.15 p.m., will be delivered simultaneously at Newcastle. The subject of the lecture will be "The Present Status of Antibiotic Therapy with Particular Reference to Aureomycin, 'Chloromycetin' and Terramycin". Professor Blake, who is Professor of Medicine at the Yale University School of Medicine, will give his lecture at the Stawell Hall, The Royal Australasian College of Physicians, 145 Macquarie Street, Sydney; the lecture at Newcastle will be given at the Australian Broadcasting Commission's studios, duplicate slides will be shown there and the Newcastle audience will be able to ask questions at the close of the lecture. This lecture at Newcastle is to be held by arrangement with the Postal Department and the Australian Broadcasting Commission. There will be no charge for admission. Further details can be obtained from Dr. A. J. Ostinga, T. and G. Building, 45 Hunter Street, Newcastle.

Obituary.

REGINALD JOHN VERCO.

WE regret to announce the death of Dr. Reginald John Verco, which occurred on June 5, 1950, at Adelaide.

ALEXANDER TENNANT CHAPPLE.

WE regret to announce the death of Dr. Alexander Tennant Chapple, which occurred on June 14, 1950, at Sydney.

GEORGE GORR.

WE regret to announce the death of Dr. George Gorr, which occurred on May 26, 1950, at Fitzroy, Victoria.

Nominations and Elections.

THE undermentioned has applied for election as a member of the South Australian Branch of the British Medical Association.

Russell, Albert William, M.B., B.S., 1949 (Univ. Adelaide), 19 Parker Street, Mile End.

The undermentioned have been elected members of the South Australian Branch of the British Medical Association:

Stoddart, Harold William Downing, M.B., B.S., 1911 (Univ. Adelaide), 26 Partridge Street, Glenelg.

Wilson, John Grenell, M.B., B.S., 1949 (Univ. Adelaide), 287 Unley Road, Malvern.

Medical Appointments.

Dr. I. B. Jose has been appointed an honorary consulting surgeon at the Royal Adelaide Hospital, Adelaide.

Dr. Rosemary Brindal has been appointed resident medical officer at the Royal Adelaide Hospital, Adelaide.

Dr. L. A. Langley and Dr. J. A. McCluskie have been appointed medical examiners of the State Psychiatric Clinic of Tasmania.

Dr. H. K. Fry has been reappointed official visitor to the Parkside Mental Hospital, South Australia.

Dr. H. E. Pellew has been appointed medical officer to the night clinic (female section) of the Royal Adelaide Hospital, Adelaide.

Dr. A. C. McEachern has been appointed honorary surgeon at the Royal Adelaide Hospital, Adelaide.

Diary for the Month.

JUNE 27.—New South Wales Branch, B.M.A.: Ethics Committee.
JUNE 28.—South Australian Branch: Annual Meeting.
JUNE 28.—Victorian Branch, B.M.A.: Council Meeting.
JUNE 29.—New South Wales Branch, B.M.A.: Branch Meeting.
JULY 4.—New South Wales Branch, B.M.A.: Council Quarterly.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135 Macquarie Street, Sydney): Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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JUL 28 1950

PUBLISHED WEEKLY

PRICE TWO SHILLINGS

THE MEDICAL JOURNAL OF AUSTRALIA

VOL. I.—37TH YEAR. SYDNEY, SATURDAY, JUNE 24, 1950. No. 25.

COMMONWEALTH OF AUSTRALIA. DEPARTMENT OF HEALTH.

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